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(54) Title: INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME

(57) Abstract

The present invention relates to novel classes of compounds which are inhibitors of interleukin-1β converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against IL-1-, apoptosis-, IGIF-, and IFN-γ- mediated diseases, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, and necrotic diseases. This invention also relates to methods for inhibiting ICE activity, for treating interleukin-1-, apoptosis-, IGIF- and IFN-γ-mediated diseases and decreasing IGIF and IFN-γ production using the compounds and compositions of this invention. This invention also relates to methods for preparing N-acylamino compounds.

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INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME

TECHNICAL FIELD OF THE INVENTION

The present invention relates to novel classes of compounds which are inhibitors of interleukin-1β converting enzyme ("ICE"). This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against interleukin-1- ("IL-1"), apoptosis-, interferon gamma inducing factor- ("IGIF") and interferon-γ- ("IFN-γ") mediated diseases, including inflammatory diseases, autoimmune diseases, destructive bone, proliferative disorders, infectious diseases and degenerative diseases. This invention also relates to methods for inhibiting ICE activity, and decreasing IGIF production and IFN-γ production and methods for treating interleukin-1-, apoptosis-, IGIF- and IFN-γ-mediated diseases using the compounds and compositions of this invention. This invention also relates to methods of preparing N-acylamino compounds.

BACKGROUND OF THE INVENTION

Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory protein that stimulates fibroblast differentiation and proliferation, the production of prostaglandins, collagenase and phospholipase by synovial cells and chondrocytes, basophil and eosinophil degranulation and neutrophil activation. Oppenheim, J.H. et al, Immunology Today, 7, pp. 45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. For example, in rheumatoid arthritis, IL-1 is both a mediator of inflammatory symptoms and of the destruction of the cartilage proteoglycan in afflicted joints. Wood, D.D. et al., Arthritis Rheum. 26, 975, (1983); Pettipher, E.J. et al., Proc. Natl. Acad. Sci. UNITED STATES OF AMERICA 71, 295 (1986); Arend, W.P. and Dayer, J.M., Arthritis Rheum. 38, 151 (1995). IL-1 is also a highly potent bone resorption agent. Jandiski, J.J., J. Oral Path 17, 145 (1988); Dewhirst, F.E. et al., J. Immunol. 8, 2562 1985). It is alternately referred to as "osteoclast activating factor" in destructive bone diseases such as osteoarthritis and multiple myeloma. Bataille, R. et al., Int. J. Clin. Lab. Res. 21(4), 283 (1992). In certain proliferative disorders, such as acute myelogenous leukemia and multiple myeloma, IL-1 can promote tumor cell growth and adhesion. Bani, M.R., J. Natl. Cancer Inst. 83, 123 (1991); Vidal-Vanaclocha, F., Cancer Res. 54, 2667 (1994). In these disorders, IL-1 also stimulates production of other cytokines such as IL-6, which can modulate tumor development (Tartour et al., Cancer Res. 54, 6243 (1994). IL-1 is predominantly produced by peripheral blood monocytes as part of the inflammatory response

and exists in two distinct agonist forms, IL-1α and IL-1β. Mosely, B.S. et al., Proc. Nat. Acad. Sci., 84, pp. 4572-4576 (1987); Lonnemann, G. et al., Eur.J. Immunol., 19, pp. 1531-1536 (1989).

IL-1β is synthesized as a biologically inactive precursor, pIL-1β. pIL-1β lacks a conventional leader sequence and is not processed by a signal peptidase. March, C.J., Nature, 315, pp. 641-647 (1985). Instead, pIL-1β is cleaved by interleukin-1β converting enzyme ("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R., et al., J. Biol. Chem., 265, pp. 14526-14528 (1992); A.D. Howard et al., J. Immunol., 147, pp. 2964-2969 (1991). ICE is a cysteine protease localized primarily in monocytes. It converts precursor IL-1β to the mature form. Black, R.A. et al., FEBS Lett., 247, pp. 386-390 (1989); Kostura, M.J. et al., Proc. Natl. Acad. Sci. UNITED STATES OF AMERICA, 86, pp. 5227-5231 (1989). Processing by ICE is also necessary for the transport of mature IL-1β through the cell membrane.

ICE, or its homologs, also appears to be involved in the regulation of programmed cell death or apoptosis. Yuan, J. et al., Cell, 75, pp. 641-652 (1993); Miura, M. et al., Cell, 75, pp. 653-660 (1993); Nett-Fiordalisi, M.A. et al., J. Cell Biochem., 17B, p. 117 (1993). In particular, ICE or ICE homologs are thought to be associated with the regulation of apoptosis in neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, Science, 259, pp. 760-762 (1993); Gagliardini, V. et al., Science, 263, pp. 826-828 (1994). Therapeutic applications for inhibition of apoptosis

may include treatment of Alzheimer's disease, Parkinson's disease, stroke, myocardial infarction, spinal atrophy, and aging.

ICE has been demonstrated to mediate apoptosis (programmed cell death) in certain tissue types. Steller, H., Science, 267, p. 1445 (1995); Whyte, M. and Evan, G., Nature, 376, p. 17 (1995); Martin, S.J. and Green, D.R., Cell, 82, p. 349 (1995); Alnemri, E.S., et al., J. Biol. Chem., 270, p. 4312 (1995); Yuan, J. Curr. Opin. Cell Biol., 7, p. 211 (1995). A transgenic mouse with a disruption of the ICE gene is deficient in Fas-mediated apoptosis (Kuida, K. et al., Science 267, 2000 (1995)). This activity of ICE is distinct from its role as the processing enzyme for pro-IL1β. It is conceivable that in certain tissue types, inhibition of ICE may not affect secretion of mature IL-1β, but may inhibit apoptosis.

Enzymatically active ICE has been previously described as a heterodimer composed of two subunits, p20 and p10 (20kDa and 10kDa molecular weight, respectively). These subunits are derived from a 45kDa proenzyme (p45) by way of a p30 form, through an activation mechanism that is autocatalytic. Thornberry, N.A. et al., Nature, 356, pp. 768-774 (1992). The ICE proenzyme has been divided into several functional domains: a prodomain (p14), a p22/20 subunit, a polypeptide linker and a p10 subunit. Thornberry et al., supra; Casano et al., Genomics, 20, pp. 474-481 (1994).

Full length p45 has been characterized by its cDNA and amino acid sequences. PCT patent applications WO 91/15577 and WO 94/00154. The p20 and p10 cDNA and amino acid sequences are also known. Thornberry et al., supra. Murine and rat ICE have also been sequenced and cloned. They have high amino acid and

nucleic acid sequence homology to human ICE. Miller, D.K. et al., Ann. N.Y. Acad. Sci., 696, pp. 133-148 (1993); Molineaux, S.M. et al., Proc. Nat. Acad. Sci., 90, pp. 1809-1813 (1993). The three-dimensional structure of ICE has been determined at atomic resolution by X-ray crystallography. Wilson, K.P., et al., Nature, 370, pp. 270-275 (1994). The active enzyme exists as a tetramer of two p20 and two p10 subunits.

Additionally, there exist human homologs of ICE with sequence similarities in the active site regions of the enzymes. Such homologs include TX (or ICE_{rel-II} or ICH-2) (Faucheu, et al., EMBO J., 14, p. 1914 (1995); Kamens J., et al., J. Biol. Chem., 270, p. 15250 (1995); Nicholson et al., J. Biol. Chem., 270 15870 (1995)), TY (or $ICE_{rel-III}$) (Nicholson et al., J. Biol. Chem., 270, p. 15870 (1995); ICH-1 (or Nedd-2) (Wang, L. et al., Cell, 78, p. 739 (1994)), MCH-2, (Fernandes-Alnemri, T. et al., Cancer Res., 55, p. 2737 (1995), CPP32 (or YAMA or apopain) (Fernandes-Alnemri, T. et al., J. Biol. Chem., 269, p. 30761 (1994); Nicholson, D.W. et al., Nature, 376, p. 37 (1995)), and CMH-1 (or MCH-3) (Lippke, et al., J. Biol. Chem., (1996); Fernandes-Alnemri, T. et al., Cancer Res., (1995)). Each of these ICE homologs, as well as ICE itself, is capable of inducing apoptosis when overexpressed in transfected cell lines. Inhibition of one or more of these homologs with the peptidyl ICE inhibitor Tyr-Val-Ala-Asp-chloromethylketone results in inhibition of apoptosis in primary cells or cell lines. Lazebnik et al., Nature, 371, p. 346 (1994). The compounds described herein are also capable of inhibiting one or more homologs of ICE (see Example 5). Therefore, these compounds may be used to inhibit apoptosis in tissue types that contain ICE homologs, but which do not contain active ICE or produce mature

IL-1β.

Interferon-gamma inducing factor (IGIF) is an approximately 18-kDa polypeptide that stimulates T-cell production of interferon-gamma (IFN-γ). IGIF is produced by activated Kupffer cells and macrophages _in vivo_ and is exported out of such cells upon endotoxin stimulation. Thus, a compound that decreases IGIF production would be useful as an inhibitor of such T-cell stimulation which in turn would reduce the levels of IFN-γ production by those cells.

IFN-γ is a cytokine with immunomodulatory effects on a variety of immune cells. In particular, IFN-γ is involved in macrophage activation and Th1 cell selection (F. Belardelli, _APMIS_, 103, p. 161 (1995)). IFN-γ exerts its effects in part by modulating the expression of genes through the STAT and IRF pathways (C. Schindler and J.E. Darnell, _Ann. Rev. Biochem._, 64, p. 621 (1995); T. Taniguchi, _J. Cancer Res. Clin. Oncol._, 121, p. 516 (1995)).

Mice lacking IFN-γ or its receptor have multiple defects in immune cell function and are resistant to endotoxic shock (S. Huang et al., _Science_, 259, p. 1742 (1993); D. Dalton et al., _Science_, 259, p. 1739 (1993); B. D. Car et al., _J. Exp. Med._, 179, p. 1437 (1994)). Along with IL-12, IGIF appears to be a potent inducer of IFN-γ production by T cells (H. Okamura et al., _Infection and Immunity_, 63, p. 3966 (1995); H. Okamura et al., _Nature_, 378, p. 88 (1995); S. Ushio et al., _J. Immunol._, 156, p. 4274 (1996)).

IFN-γ has been shown to contribute to the pathology associated with a variety of inflammatory, infectious and autoimmune disorders and diseases. Thus, compounds capable of decreasing IFN-γ production

would be useful to amelicrate the effects of IFN-γ related pathologies.

The biological regulation of IGIF and thus IFN-γ has not been elucidated. It is known that IGIF is synthesized as a precursor protein, called "pro-IGIF". It has been unclear, however, how pro-IGIF is cleaved and whether its processing has biological importance.

Accordingly, compositions and methods capable of regulating the conversion of pro-IGIF to IGIF would be useful for decreasing IGIF and IFN-γ production _in vivo_, and thus for ameliorating the detrimental effects of these proteins which contribute to human disorders and diseases.

However, ICE and other members of the ICE/CED-3 family have not previously been linked to the conversion of pro-IGIF to IGIF or to IFN-γ production _in vivo_.

ICE inhibitors represent a class of compounds useful for the control of inflammation or apoptosis or both. Peptide and peptidyl inhibitors of ICE have been described. PCT patent applications WO 91/15577; WO 93/05071; WO 93/09135; WO 93/14777 and WO 93/16710; and European patent application 0 547 699. Such peptidyl inhibitors of ICE has been observed to block the production of mature IL-1β in a mouse model of inflammation (vide infra) and to suppress growth of leukemia cells *in vitro* (Estrov et al., _Blood_ 84, 380a (1994)). However, due to their peptidic nature, such inhibitors are typically characterized by undesirable pharmacologic properties, such as poor cellular penetration and cellular activity, poor oral absorption, poor stability and rapid metabolism. Plattner, J.J. and D.W. Norbeck, in _Drug Discovery_

Technologies, C.R. Clark and W.H. Moos, Eds. (Ellis Horwood, Chichester, England, 1990), pp. 92-126. This has hampered their development into effective drugs.

Non-peptidyl compounds have also been reported to inhibit ICE in vitro. PCT patent application WO 95/26958; US Patents 5,552,400; Dolle et al., J. Med. Chem., 39, pp. 2438-2440 (1996); However, it is not clear whether these compounds have the appropriate pharmacological profile to be therapeutically useful.

Additionally, current methods for the preparation of such compounds are not advantageous. These methods use tributyltin hydride, a toxic, moisture sensitive reagent. Thus, these methods are inconvenient to carry out, pose a health risk and create toxic-waste disposal problems. Furthermore, it is difficult to purify compounds prepared by these methods.

Accordingly, the need exists for compounds that can effectively inhibit the action of ICE *in vivo*, for use as agents for preventing and treating chronic and acute forms of IL-1-mediated diseases, apoptosis-, IGIF-, or IFN-γ-mediated diseases, as well as inflammatory, autoimmune, destructive bone, proliferative, infectious, or degenerative diseases. The need also exists for methods of preparing such compounds.

SUMMARY OF THE INVENTION

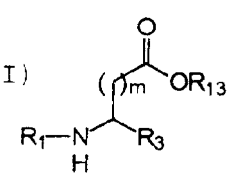
The present invention provides novel classes of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of ICE. These compounds can be used alone or in combination with other therapeutic or prophylactic agents, such as antibiotics, immunomodulators or other anti-inflammatory agents, for the treatment or

prophylaxis of diseases mediated by IL-1, apoptosis, IGIF or IFN-γ. According to a preferred embodiment, the compounds of this invention are capable of binding to the active site of ICE and inhibiting the activity of that enzyme. Additionally, they have improved cellular potency, improved pharmacokinetics, and/or improved oral bioavailability compared to peptidyl ICE inhibitors.

It is a principal object of this invention to provide novel classes of compounds which are inhibitors of ICE represented by formulas:

α $$R_1\text{-NH-}X_1\begin{array}{l}/(CJ_2)_m\text{-}T\\ \backslash(CH_2)_g\text{-}R_3\end{array}$$;

(I), (VI) $$R_1\text{-}\underset{\displaystyle H}{\underset{|}{N}}\text{-}R_2$$; and

(II)-(V) and (VII)  ;

wherein the various substituents are described herein.

It is a further object of this invention to provide a process of preparing N-acylamino compounds by coupling a carboxylic acid with an alloc-protected amine.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A ICE cleaves pro-IGIF in vivo. Cell lysates from Cos cells transfected with the various indicated expression plasmids or controls were analyzed for the presence of IGIF by separating proteins by SDS-PAGE and immunoblotting with anti-IGIF antisera (lane 1, mock transfected cells; lane 2, pro-IGIF alone; lanes 3-12, pro-IGIF in combination with ICE, ICE-C285S, CPP32, CPP32-C163S, CMH-1, CMH-1-C186S, Tx, Tx-C258S, respectively). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular weight markers in kDa are shown on the left (Example 23).

Fig. 1B ICE cleaves pro-IGIF at the authentic processing site in vitro as shown by Coomassie blue staining of proteolytic reaction products separated by SDS-PAGE (Example 23). The proteases and inhibitors used were: lane 1, buffer control; lane 2, 0.1 nM ICE; lane 3, 1 nM ICE; lanes 4 and 5, 1 nM ICE with 10 nM Cbz-Val-Ala-Asp-[(2,6-dichlorobenzoyl)oxy]methyl ketone and 100 nM Ac-Tyr-Val-Ala-Asp-aldehyde, respectively; lanes 6 and 7, 15 nM CPP32 with and without 400 nM Ac-Asp-Glu-Val-Asp-aldehyde (D. W. Nicholson et al., Nature, 376, p. 37 (1995)), respectively; lane 8, 100 nM CMH-1; lane 9, 10 units/ml granzyme B; and M, molecular weight markers in kDa.

Fig. 1C ICE cleavage converts inactive pro-IGIF to active IGIF which induces IFN-γ production in Th1 helper cells. Uncleaved (Pro-IGIF), ICE-cleaved (Pro-IGIF/ICE), CPP32-cleaved (Pro-IGIF/CPP32), and recombinant mature IGIF (rIGIF) were incubated with

A.E7 Th1 cells at 12 ng/ml (open bar) and 120 ng/ml (hatched bar) for eighteen hours and the levels of IFN-γ released into the culture medium assayed by ELISA (Example 23). A.E7 cells cultured with buffer, ICE alone (ICE) or CPP32 alone (CPP32) were assayed similarly for negative controls. The numbers represent the average of three determinations.

Fig. 2A Mature IGIF (18-kDa) is produced by Cos cells co-transfected with pro-IGIF and ICE-expressing plasmids. Cell lysates (left) and conditioned medium (right) from Cos cells transfected with a pro-IGIF expression plasmid in the absence (-) or presence of an expression plasmid encoding wild type (ICE) or inactive mutant (ICE-C285S) ICE. Transfected cells were metabolically labeled with ^{35}S-methionine, proteins from cell lysates and conditioned medium immunoprecipitated with anti-IGIF antisera and separated by SDS-PAGE (Example 24). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular weight markers in kDa are shown on the left.

Fig. 2B IFN-γ inducing activity is detected in Cos cells co-transfected with pro-IGIF and ICE-expressing plasmids. Cell lysates (hatched bar) and conditioned medium (open bar) from Cos cells transfected with a pro-IGIF expression plasmid in the absence (Pro-IGIF) or presence (Pro-IGIF/ICE) of an expression plasmid encoding wild type (ICE) were assayed for IFN-γ levels (ng/ml) by ELISA. Cos cells transfected with buffer (Mock) or an ICE-expressing plasmid alone (ICE) served as negative controls (Example 24).

Fig. 3A Kupffer cells from mice lacking ICE are defective in the export of IGIF. Kupffer cells from wild type mice (ICE +/+) or ICE-deficient mice homozygous for an ICE mutation (ICE-/-) were isolated and primed with LPS for three hours. The levels of immunoreactive IGIF polypeptides in the conditioned media (ng/ml) of wild type cells were measured by ELISA (Example 25). N.D. (not detectable) indicates that the IGIF concentration was less than 0.1 ng/ml.

Fig. 3B Kupffer cells from mice lacking ICE are defective in the export of mature IGIF. Kupffer cells from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were isolated and primed with LPS for three hours. Primed cells were metabolically labeled with ^{35}S-methionine, proteins from cell lysates and conditioned medium immunoprecipitated with anti-IGIF antisera and separated by SDS-PAGE (Example 25). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular mass markers in kDa are shown on the left.

Fig. 3C Serum from ICE-deficient mice contains reduced levels of IGIF. Serum samples from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were assayed for IGIF levels (ng/ml) by ELISA (Example 25).

Fig. 3D Serum from ICE-deficient mice contains reduced levels of IFN-γ. Serum samples from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were assayed for IFN-γ levels (ng/ml) by ELISA (Example 25).

Fig. 4 Serum IFN-γ levels are significantly reduced in ICE-deficient mice after an acute challenge with LPS (Example 26). Serum samples from wild type mice (filled squares) or ICE-deficient mice (filled circles) were assayed for IFN-γ levels (ng/ml) by ELISA as a function of time (hours) after LPS challenge. Temperatures of the animals during the time course in degrees Celcius is shown for wild type mice (open squares) or ICE-deficient mice (open circles).

Fig. 5 The ICE inhibitor, AcYVAD-aldehyde (AcYVAD-CHO), inhibits LPS-stimulated IL-1ß and IFN-γ synthesis by human peripheral blood mononuclear cells (PBMC). Percent (%) inhibition as a function of inhibitor concentration (μM) is shown for IL-1ß (open squares) and IFN-γ (open diamonds) synthesis.

Fig. 6 Compound **214e** inhibits IL-1β production in LPS-challenged mice. Serum samples from CD1 mice were assayed for IL-1β levels (pg/ml) by ELISA after LPS challenge. Compound **214e** was administered by intraperitoneal (IP) injection one hour after LPS challenge. Blood was collected seven hours after LPS challenge (see Example 7).

Fig. 7 Compound **217e** inhibits IL-1β production in LPS-challenged mice. Serum samples from CD1 mice were assayed for IL-1β levels (pg/ml) by ELISA after LPS challenge. Compound **217e** was administered by intraperitoneal (IP) injection one hour after LPS challenge. Blood was collected seven hours after LPS challenge (see Example 7).

Fig. 8 Compound **214e**, but not compound **217e**,

inhibits IL-1β production in LPS-challenged mice when administered by oral gavage. This assay measures oral absorption under similar conditions as those described for Figs. 6 and 7. These results indicates that **214e** is potentially orally active as an ICE inhibitor (see Example 7).

Fig. 9 Compound **214e** and analogs of **214e** also inhibit IL-1β production after IP administration. These results were obtained in the assay described for **Figs. 6** and **7** and Example 7.

Fig. 10 Compound **214e**, and analogs of **214e**, also inhibit IL-1β production after oral (PO) administration. These results were obtained in the assay described for **Figs. 6** and **7** and Example 7.

Figs. 11A/B Compounds **302** and **304a** show detectable blood levels when administered orally (50mg/kg, in 0.5 % carboxymethylcellulose) to mice. Blood samples were collected at 1 and 7 hours after dosing. Compounds **302** and **304a** are prodrugs of **214e** and are metabolized to **214e** <u>in</u> <u>vivo</u>. Compound **214e** shows no blood levels above 0.10 μg/ml when administered orally (Example 8).

Fig. 12 Compound **412f** blocks the progression of type II collagen-induced arthritis in male DBA/1J mice (Wooley, P.H., <u>Methods in Enzymology</u>, 162, pp. 361-373 (1988) and Geiger, T., <u>Clinical and Experimental Rheumatology</u>, 11, pp. 515-522 (1993)). Compound **412f** was administered twice a day (10, 25 and 50mg/kg), approximately 7h apart, by oral gavage. Inflammation was measured on the Arthritis Severity Score on a 1 to 4 scale of increasing severity. The scores of the two front paws were added to give the final score (see Example 21).

Fig. 13 Compound **412d** blocks the progression of type II collagen-induced arthritis in male DBA/1J mice. The results were obtained as described for **Fig. 12** and in Example 21.

Fig. 14 Compound **696a** blocks the progression of type II collagen-induced arthritis in male DBA/1J mice. The results were obtained as described for **Fig. 12** and in Example 21.

ABBREVIATIONS AND DEFINITIONS

Abbreviations

Designation	Reagent or Fragment
Ala	alanine
Arg	arginine
Asn	asparagine
Asp	aspartic acid
Cys	cysteine
Gln	glutamine
Glu	glutamic acid
Gly	glycine
His	histidine
Ile	isoleucine
Leu	leucine
Lys	lysine
Met	methionine
Phe	phenylalanine
Pro	proline
Ser	serine
Thr	threonine
Trp	tryptophan
Tyr	tyrosine
Val	valine
Ac_2O	acetic anhydride
n-Bu	normal-butyl

DMF	dimethylformamide
DIEA	*N,N*-diisopropylethylamine
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_2O	diethyl ether
EtOAc	ethyl acetate
Fmoc	9-fluorenylmethyoxycarbonyl
HBTU	O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOBT	1-hydroxybenzotriazole hydrate
MeOH	methanol
TFA	trifluoroacetic acid
Alloc	allyloxycarbonyl

Definitions

The following terms are employed herein:

The term "interferon gamma inducing factor" or "IGIF" refers to a factor which is capable of stimulating the endogenous production of IFN-γ.

The term "ICE inhibitor" refers to a compound which is capable of inhibiting the ICE enzyme. ICE inhibition may be determined using the methods described and incorporated by reference herein. The skilled practitioner realizes that an in vivo ICE inhibitor is not necessarily an in vitro ICE inhibitor. For example, a prodrug form of a compound typically demonstrates little or no activity in in vitro assays. Such prodrug forms may be altered by metabolic or other biochemical processes in the patient to provide an in vivo ICE inhibitor.

The term "cytokine" refers to a molecule which mediates interactions between cells.

The term "condition" refers to any disease,

disorder or effect that produces deleterious biological consequences in a subject.

The term "subject" refers to an animal, or to one or more cells derived from an animal. Preferably, the animal is a mammal, most preferably a human. Cells may be in any form, including but not limited to cells retained in tissue, cell clusters, immortalized cells, transfected or transformed cells, and cells derived from an animal that have been physically or phenotypically altered.

The term "active site" refers to any or all of the following sites in ICE: the substrate binding site, the site where an inhibitor binds and the site where the cleavage of substrate occurs.

The term "heterocycle" or "heterocyclic" refers to a stable mono- or polycyclic compound which may optionally contain one or two double bonds or may optionally contain one or more aromatic rings. Each heterocycle consists of carbon atoms and from one to four heteroatoms independently selected from a group including nitrogen, oxygen, and sulfur. As used herein, the terms "nitrogen heteroatoms" and "sulphur heteroatoms" include any oxidized form of nitrogen or sulfur and the quaternized form of any basic nitrogen. Heterocycles defined above include, for example, pyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinonlinyl, purinyl, pyrimidyl, indolinyl, benzimidazolyl, imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, β-carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl, oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl,

tetrahydropyranyl, tetrahydrofuranyl, thiadiazolyl, benzodioxolyl, benzothienyl, tetrahydrothiophenyl and sulfolanyl. Further heterocycles are described in A.R. Katritzky and C.W. Rees, eds., Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Use of Heterocyclic Compounds, Vol. 1-8, Pergamon Press, NY (1984).

The term "cycloalkyl" refers to a mono- or polycyclic group which contains 3 to 15 carbons and may optionally contain one or two double bonds. Examples include cyclohexyl, adamantyl and norbornyl.

The term "aryl" refers to a mono- or polycyclic group which contains 6, 10, 12, or 14 carbons in which at least one ring is aromatic. Examples include phenyl, naphthyl, and tetrahydronaphthalene.

The term "heteroaromatic" refers to a mono- or polycyclic group which contains 1 to 15 carbon atoms and from 1 to 4 heteroatoms, each of which is selected independently from a group including sulphur, nitrogen and oxygen, and which additionally contains from 1 to 3 five or six membered rings, at least one of which is aromatic.

The term "alpha-amino acid" (α-amino acid) refers to both the naturally occurring amino acids and other "non-protein" α-amino acids commonly utilized by those in the peptide chemistry arts when preparing synthetic analogues of naturally occurring peptides, including D and L forms. The naturally occurring amino acids are glycine, alanine, valine, leucine, iso-leucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ-carboxyglutamic acid, arginine, ornithine and lysine. Examples of "non-protein" alpha-amino acids include

hydroxylysine, homoserine, homotyrosine, homophenylalanine, citrulline, kynurenine, 4-aminophenylalanine, 3-(2-naphthyl)-alanine, 3-(1-naphthyl)-alanine, methionine sulfone, t-butyl-alanine, t-butylglycine, 4-hydroxyphenylglycine, aminoalanine, phenylglycine, vinylalanine, propargyl-glycine, 1,2,4-triazolo-3-alanine, 4,4,4-trifluoro-threonine, thyronine, 6-hydroxytryptophan, 5-hydro-xytryptophan, 3-hydroxykynurenine, 3-aminotyrosine, trifuoromethylalanine, 2-thienylalanine, (2-(4-pyridyl)ethyl)-cysteine, 3,4-dimethoxy-phenylalanine, 3-(2-thiazolyl)-alanine, ibotenic acid, 1-amino-1-cyclopentanecarboxylic acid, 1-amino-1-cyclohexanecarboxylic acid, quisqualic acid, 3-trifluoromethylphenylalanine, 4-trifluoro-methylphenylalanine, cyclohexylalanine, cyclo-hexylglycine, thiohistidine, 3-methoxytyrosine, elastatinal, norleucine, norvaline, alloisoleucine, homoarginine, thioproline, dehydroproline, hydroxyproline, isonipectotic acid, homoproline, cyclohexylglycine, α-amino-n-butyric acid, cyclohexylalanine, aminophenylbutyric acid, phenylalanines substituted at the ortho, meta, or para position of the phenyl moiety with one or two of the following: a (C_1-C_4) alkyl, a (C_1-C_4) alkoxy, halogen or nitro groups or substituted with a methylenedioxy group; β-2- and 3-thienylalanine, β-2- and 3-furanylalanine, β-2-, 3- and 4-pyridylalanine, β-(benzothienyl-2- and 3-yl)alanine, β-(1- and 2-naphthyl)alanine, O-alkylated derivatives of serine, threonine or tyrosine, S-alkylated cysteine, S-alkylated homocysteine, O-sulfate, O-phosphate and O-carboxylate esters of tyrosine, 3-sulfo-tyrosine, 3-carboxy-tyrosine, 3-phospho-tyrosine, 4-methane sulfonic acid ester of tyrosine, 4-methane phosphonic acid ester of tyrosine, 3,5-diiodotyrosine, 3-nitrotyrosine, ε-alkyl lysine, and delta-alkyl ornithine.

Any of these α-amino acids may be substituted with a methyl group at the alpha position, a halogen at any aromatic residue on the α-amino side chain, or an appropriate protective group at the O, N, or S atoms of the side chain residues. Appropriate protective groups are disclosed in "Protective Groups In Organic Synthesis," T.W. Greene and P.G.M. Wuts, J. Wiley & Sons, NY, NY, 1991.

The term "substitute" refers to the replacement of a hydrogen atom in a compound with a substituent group. In the present invention, those hydrogen atoms which form a part of a hydrogen bonding moiety which is capable of forming a hydrogen bond with the carbonyl oxygen of Arg-341 of ICE or the carbonyl oxygen of Ser-339 of ICE are excluded from substitution. These excluded hydrogen atoms include those which comprise an -NH- group which is alpha to a -CO- group and are depicted as -NH- rather than an X group or some other designation in the following diagrams: (a) through (t), (v) through (z).

The term "straight chain" refers to a contiguous unbranching string of covalently bound atoms. The straight chain may be substituted, but these substituents are not a part of the straight chain.

The term "K_i" refers to a numerical measure of the effectiveness of a compound in inhibiting the activity of a target enzyme such as ICE. Lower values of K_i reflect higher effectiveness. The K_i value is a derived by fitting experimentally determined rate data to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The term "patient" as used in this application refers to any mammal, especially humans.

The term "pharmaceutically effective amount" refers to an amount effective in treating or

ameliorating an IL-1-, apoptosis-, IGIF- or IFN-γ-mediated disease in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially lessening IL-1-, apoptosis-, IGIF or IFN-γ mediated diseases in a patient.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a non-toxic carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this invention or any other compound which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an anti-ICE active metabolite or residue thereof.

Pharmaceutically acceptable salts of the compounds of this invention include, for example, those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and $N-(C_{1-4}\ alkyl)_4^+$

salts.

This invention also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

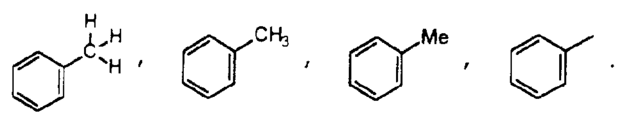
The ICE inhibitors of this invention may contain one or more "asymmetric" carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although specific compounds and scaffolds exemplified in this application may be depicted in a particular stereochemical configuration, compounds and scaffolds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

The ICE inhibitors of this invention may comprise ring structures which may optionally be substituted at carbon, nitrogen or other atoms by various substituents. Such ring structures may be singly or multiply substituted. Preferably, the ring structures contain between 0 and 3 substituents. When multiply substituted, each substituent may be picked independently of any other substituent as long as the

combination of substituents results in the formation of a stable compound.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

Substituents may be represented in various forms. These various forms are known to the skilled practitioner and may be used interchangeably. For example, a methyl substituent on a phenyl ring may be represented in any of the following forms:



Various forms of substituents such as methyl are used herein interchangeably.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth.

The ICE inhibitors of one embodiment (A) of this invention are those of formula α:

$$\alpha \qquad R_1\text{-NH-}X_1 \begin{matrix} / (CJ_2)_m\text{-}T \\ \backslash (CH_2)_g\text{-}R_3 \end{matrix}$$

wherein:

X_1 is -CH;

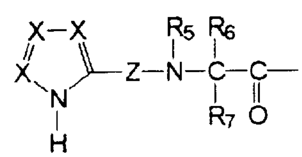
g is 0 or 1;

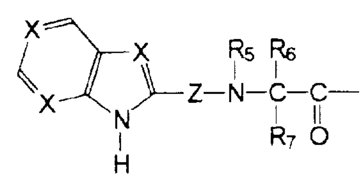
each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

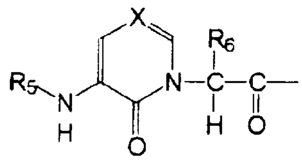
m is 0, 1, or 2;

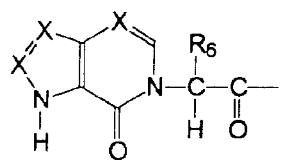
T is -OH, -CO-CO_2H, -CO_2H, or any bioisosteric replacement for -CO_2H;

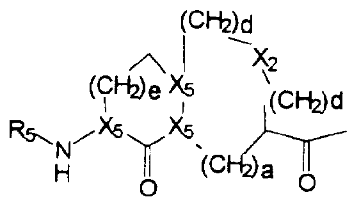
R_1 is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q_1, at any nitrogen by R_5, or at any atom by =O, -OH, -CO_2H, or halogen; any saturated ring may optionally be unsaturated at one or two bonds; and wherein R_1 (e) and R_1 (y) are optionally benzofused;

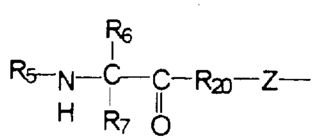
(a)  ;

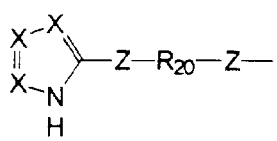
(b)  ;

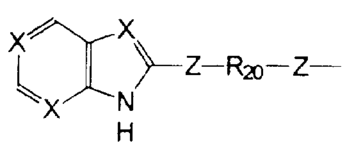
(c)  ;

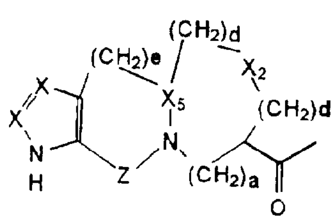
(d)  ;

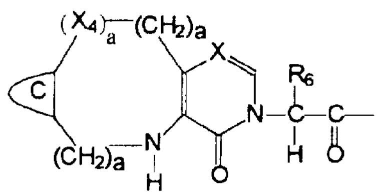
(e)  ;

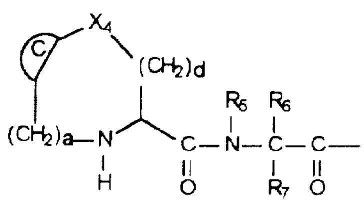
(f)  ;

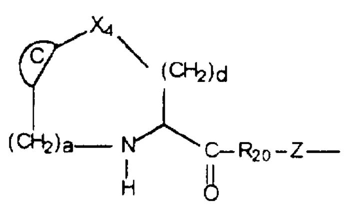
(g)  ;

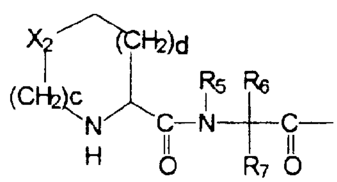
(h)  ;

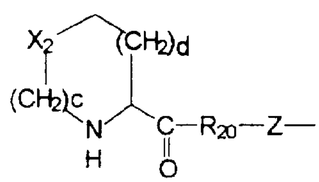
(i)  ;

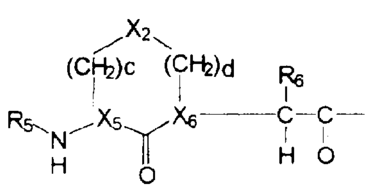
(j)  ;

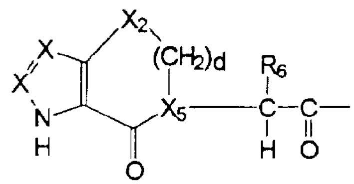
(k)  ;

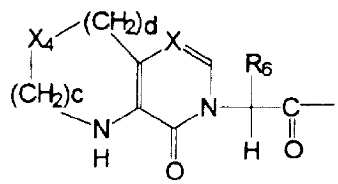
(l)  ;

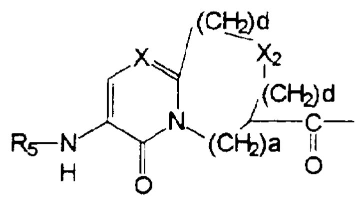
(m)  ;

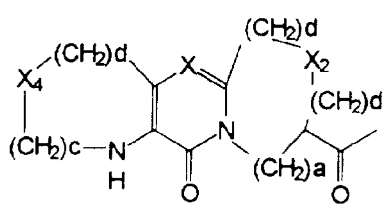
(n)  ;

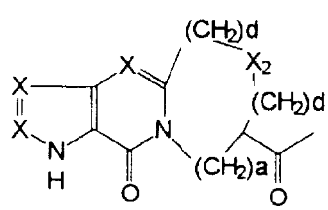
(o)  ;

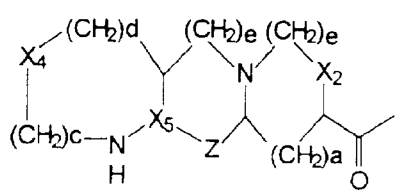
(p)  ;

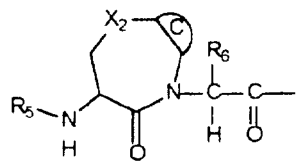
(q)  ;

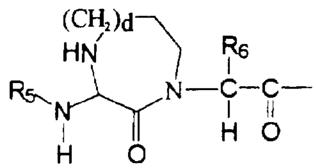
(r)  ;

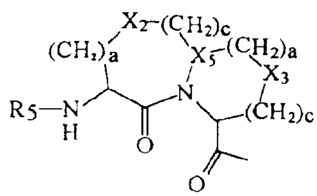
(s)  ;

(t)  ;

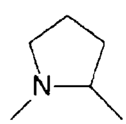
(v)  ;

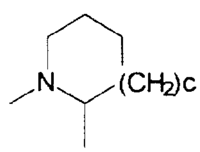
(w)  ;

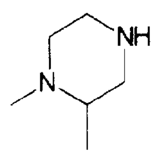
(x)  ;

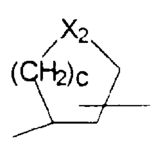
(y)  ;

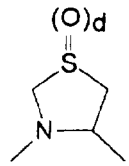
R_{20} is selected from the group consisting of:

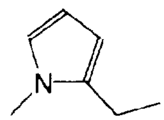
(aa1)  ;

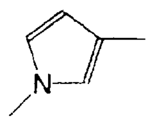
(aa2)  ;

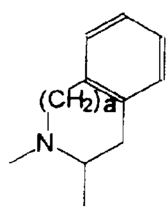
(aa3)  ;

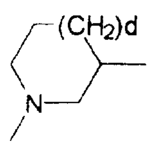
(aa4)  ;

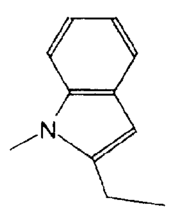
(aa5)  ;

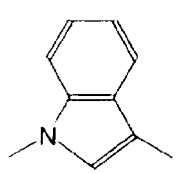
(bb)  ;

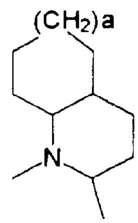
(cc)  ;

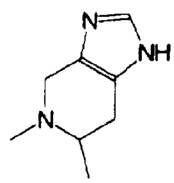
(dd)  ;

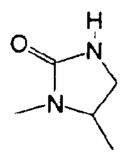
(ee)  ;

(ff)  ;

(gg)  ;

(gga)  ;

(ggb)  ; and

(ggc)  ;

wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is:

-CN,

$-CH=CH-R_9$,

$-CH=N-O-R_9$,

$-(CH_2)_{1-3}-T_1-R_9$,

$-CJ_2-R_9$,

$-CO-R_{13}$, or

$-CO-CO-N\begin{matrix}/R_5 \\ \backslash R_{10}\end{matrix}$;

each R_4 is independently selected from the group consisting of:

-H,

$-Ar_1$,

$-R_9$,

$-T_1-R_9$, and

$-(CH_2)_{1,2,3}-T_1-R_9$;

each T_1 is independently selected from the group consisting of:

$CH=CH-$,

$-O-$,

$-S-$,

$-SO-$,

$-SO_2-$,

$-NR_{10}-$,

$-NR_{10}-CO-$,

$-CO-$,

$-O-CO-$,

$-CO-O-$,

$-CO-NR_{10}-$,

$-O-CO-NR_{10}-$,

$-NR_{10}-CO-O-$,

$-NR_{10}-CO-NR_{10}-$,

$-SO_2-NR_{10}-$,

$-NR_{10}-SO_2-$, and

$-NR_{10}-SO_2-NR_{10}-$;

each R_5 is independently selected from the group consisting of:

$-H$,

$-Ar_1$,

$-CO-Ar_1$,

$-SO_2-Ar_1$,

$-CO-NH_2$,

$-SO_2-NH_2$,

$-R_9$,

$-CO-R_9$,

$-CO-O-R_9$,

$-SO_2-R_9$,

$$-CO-N\begin{matrix}/Ar_1\\ \backslash R_{10},\end{matrix}$$

$$-SO_2-N\begin{matrix}/Ar_1\\ \backslash R_{10},\end{matrix}$$

$$-CO-N\begin{matrix}/R_9\\ \backslash R_{10},\end{matrix}$$ and

$$-SO_2-N\begin{matrix}/R_9\\ \backslash R_{10};\end{matrix}$$

R_6 and R_7 taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-; or R_7 is -H and R_6 is

-H

$-Ar_1$,

$-R_9$,

$-(CH_2)_{1,2,3}-T_1-R_9$, or

an α-amino acid side chain residue;

each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted with -OH, -F, or =O and optionally substituted with one or two Ar_1 groups;

each R_{10} is independently selected from the group consisting of -H or a C_{1-6} straight or branched alkyl group;

each R_{13} is independently selected from the group consisting of $-Ar_2$, $-R_4$ and $-N(OH)-R_5$;

each Ar_1 is a cyclic group independently selected

from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, $-SO_2-$, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted with $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN,

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                                          O
                                         / \
=O, -OH, -perfluoro C1-3 alkyl,             CH2,   or -Q1;
                                         \ /
                                          O
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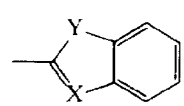
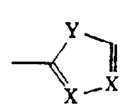
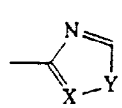
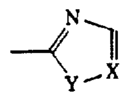
each Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ and $-Q_2$:

(hh)  ;

(ii)  ;

(jj)  ; and

(kk)  ;

each Q_1 is independently selected from the group consisting of:

$-Ar_1$

$-O-Ar_1$

$-R_9$,

$-T_1-R_9$, and

$-(CH_2)_{1,2,3}-T_1-R_9$;

each Q_2 is independently selected from the group consisting of -OH, $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, $-CF_3$, and

```
  O
 / \
    CH2;
 \ /
  O
```

provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1;

each X is independently selected from the group consisting of =N-, and =CH-;

each X_2 is independently selected from the group consisting of -O-, $-CH_2-$, -NH-, -S-, -SO-, and $-SO_2-$;

each X_3 is independently selected from the group consisting of $-CH_2-$, -S-, -SO-, and $-SO_2-$;

each X_4 is independently selected from the group consisting of $-CH_2-$ and -NH-;

each X_5 is independently selected from the group consisting of $-\underset{|}{\text{CH}}-$ and $-\underset{|}{\text{N}}-$;

X_6 is -CH- or -N-;

each Y is independently selected from the group consisting of -O-, -S-, and -NH;

each Z is independently CO or SO_2;

each a is independently 0 or 1;

each c is independently 1 or 2;

each d is independently 0, 1, or 2; and

each e is independently 0, 1, 2, or 3;

provided that when

R_1 is (f),

R_6 is an α-amino acid side chain residue, and

R_7 is -H,

then (aa1) and (aa2) must be substituted with Q_1;

also provided that when

R_1 is (o),

g is 0,

J is -H,

m is 1,

R_6 is an α-amino acid side chain residue,

R_7 is -H,

X_2 is $-CH_2-$,

X_5 is $-\underset{|}{\text{CH}}-$,

X_6 is $-\underset{|}{\text{N}}-$, and

R_3 is $-\text{CO-N}\begin{smallmatrix}/R_{10}\\ \backslash R_{10}\end{smallmatrix}$, or $-CO-R_{13}$, when

R_{13} is:

$-CH_2-O-CO-Ar_1$,

$-CH_2-S-CO-Ar_1$,

$-CH_2-O-Ar_1$,

$-CH_2-S-Ar_1$, or

$-R_4$ when $-R_4$ is -H;

then the ring of the R_1(o) group must be substituted with Q_1 or benzofused; and

provided that when

R_1 is (w),

g is 0,

J is -H,

m is 1,

T is $-CO_2H$,

X_2 is O,

R_5 is benzyloxycarbonyl, and

ring C is benzo,

then R_3 cannot be $-CO-R_{13}$ when:

R_{13} is $-CH_2-O-Ar_1$ and

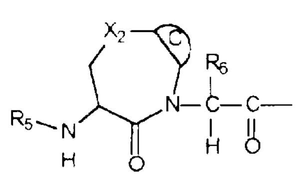
Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with a chlorine atom;

or when

R_{13} is $-CH_2-O-CO-Ar_1$, wherein

Ar_1 is 2,6-dichlorophenyl.

Preferred compounds of embodiment A employ formula α, wherein R_1 is (w):

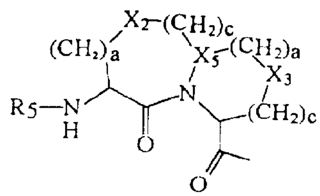
(w) 

,

wherein the other substituents are as described

above.

Other preferred compounds of embodiment A employ formula α, wherein R_1 is (y):

(y) 

wherein the other substituents are as described above.

More preferred compounds of embodiment A employ formula α, wherein:

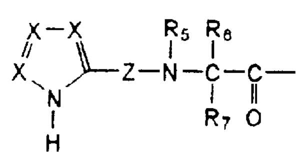
X_1 is -CH;

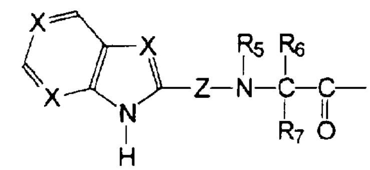
g is 0;

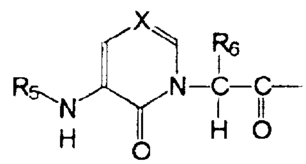
J is -H;

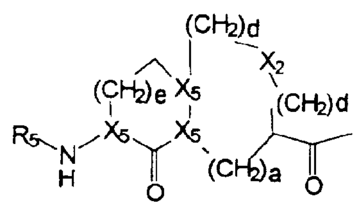
m is 0 or 1 and T is -CO-CO_2H, or any bioisosteric replacement for -CO_2H, or
m is 1 and T is -CO_2H;

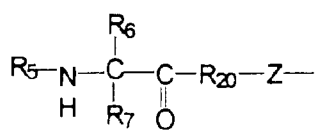
R_1 is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q_1, at any nitrogen by R_5, or at any atom by =O, -OH, -CO_2H, or halogen, and wherein (e) is optionally benzofused:

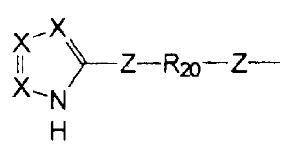
(a) 

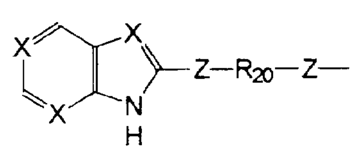
(b)  ,

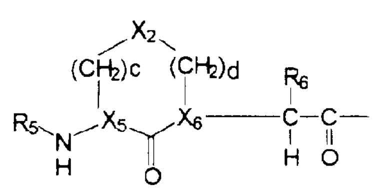
(c)  ,

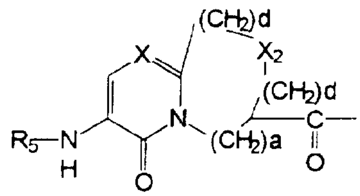
(e)  ,

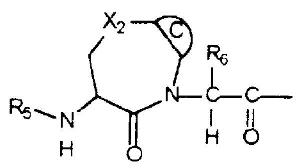
(f)  ,

(g)  ,

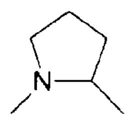
(h)  ,

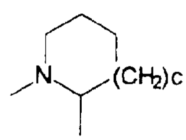
(o)  ,

(r)  , and

(w)  ;

R_{20} is:

(aa1)  , or

(aa2) 

and c is 1;

ring C is benzo optionally substituted with $-C_{1-3}$ alkyl, $-O-C_{1-3}$ alkyl, -Cl, -F or $-CF_3$;

when R_1 is (a) or (b), R_5 is preferably -H, and

when R_1 is (c), (e), (f), (o), (r), (w), (x) or (y), R_5 is preferably:

$-CO-Ar_1$
$-SO_2-Ar_1$,
$-CO-NH_2$,
$-CO-NH-Ar_1$
$-CO-R_9$,
$-CO-O-R_9$,

$-SO_2-R_9$, or
$-CO-NH-R_9$,

R_7 is -H and R_6 is: -H,
$-R_9$, or
$-Ar_1$;

R_9 is a C_{1-6} straight or branched alkyl group optionally substituted with =O and optionally substituted with $-Ar_1$;

R_{10} is -H or a $-C_{1-3}$ straight or branched alkyl group;

Ar_1 is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl optionally substituted with $-O-C_{1-3}$ alkyl, $-NH-C_{1-3}$ alkyl, $-N-(C_{1-3}$ alkyl$)_2$, -Cl, -F, $-CF_3$, $-C_{1-3}$ alkyl, or

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 O
/ \
   CH2  ;
\ /
 O
```

Q_1 is R_9 or $-(CH_2)_{0,1,2}-T_1-(CH_2)_{0,1,2}-Ar_1$, wherein T_1 is -O- or -S-;

each X is independently selected from the group consisting of =N-, and =CH-;

each X_2 is independently selected from the group consisting of -O-, $-CH_2-$, -NH-, -S-, -SO-, and $-SO_2-$;

each X_5 is independently selected from the group consisting of -CH- and -N-;

X_6 is -CH- or -N-,

provided that when:

R_1 is (o),

X_2 is $-CH_2-$,

X_5 is $-\underset{|}{C}H-$, and

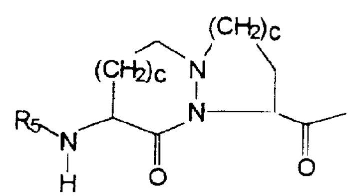
X_6 is $-\underset{|}{N}-$,

then the ring of the R_1(o) group must be substituted with Q_1 or benzofused; and

Z is C=O.

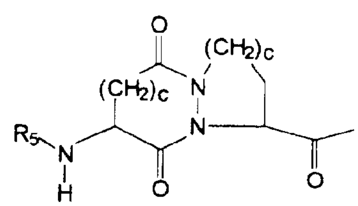
Most preferably, compounds of this more preferred embodiment are those wherein the R_1 group is:

(e1)



, or

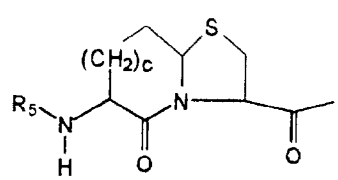
(e2)



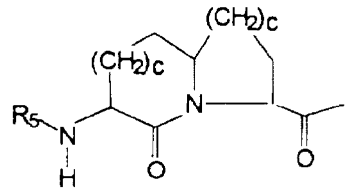
,

and c is 2; or

(e4)



, or

(e7) 

which is optionally benzofused, and c is 1 or 2;

provided that when R_1 is (e4),

g is 0,

J is -H,

m is 1,

T is $-CO_2H$,

R_5 is benzyloxycarbonyl, and

c is 1,

then R_3 cannot be $-CO-R_{13}$ when

R_{13} is $-CH_2-O-Ar_1$ and

Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl, wherein the phenyl is optionally substituted with a chlorine atom; or when

R_{13} is $-CH_2-O-CO-Ar_1$, wherein

Ar_1 is 2,6-dichlorophenyl,

and when the 2-position of the scaffold ring is substituted with para-fluoro-phenyl; and

also provided that when

R_1 is (e7),

g is 0,

J is -H,

m is 1,

T is $-CO_2H$ or -CO-NH-OH,

R_5 is a protective group for the N atom of an amino acid side chain residue, and

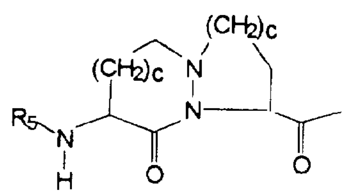
each c is 1,

then R_3 cannot be $-CO-R_{13}$ when
R_{13} is:
$-CH_2-O-CO-Ar_1$,
$-CH_2-S-CO-Ar_1$,
$-CH_2-O-Ar_1$, or
$-CH_2-S-Ar_1$.

The most preferred compounds of this embodiment are those wherein:

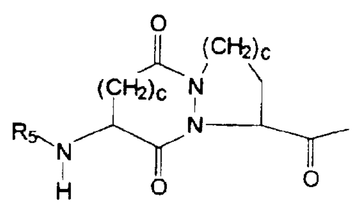
R_1 is:

(e1)



, or

(e2)



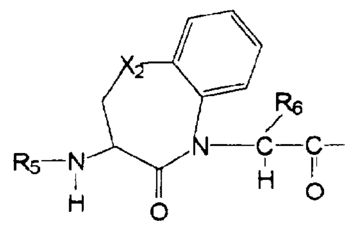
,

and c is 2;
m is 1;
T is $-CO_2H$; and
R_3 is $-CO-R_{13}$.

Other most preferred compounds of this embodiment are those wherein:

R_1 is:

(w1)



; wherein

X_2 is:

-O- ,

-S- ,

$-SO_2-$, or

-NH-;

optionally substituted with R_5 or Q_1 at X_2 when X_2 is -NH-; and

ring C is benzo substituted with $-C_{1-3}$ alkyl, $-O-C_{1-3}$ alkyl, -Cl, -F or $-CF_3$.

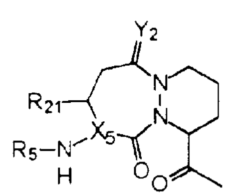
The ICE inhibitors of another embodiment (B) of this invention are those of formula (I):

$$(\underline{I}) \qquad R_1\text{-}\underset{\displaystyle H}{\underset{|}{N}}\text{-}R_2$$

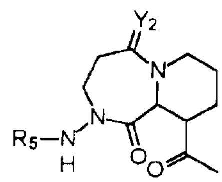
wherein:

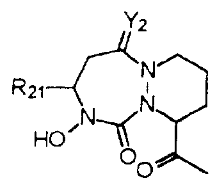
R_1 is selected from the group consisting of the following formulae:

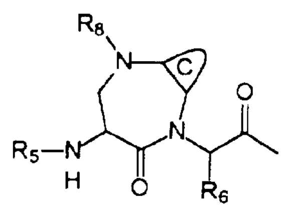
(e10)

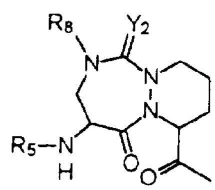


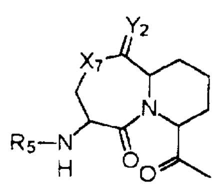
;

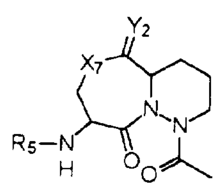
(e11)  ;

(e12)  ;

(w2)  ;

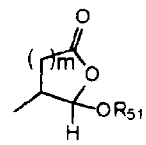
(y1)  ;

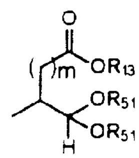
(y2)  ;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_2 is:

(a)  , or

(b)  ;

m is 1 or 2;

R_5 is selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9,

$$-C(O)-N\begin{matrix} / R_{10} \\ \backslash R_{10} \end{matrix},$$

-S(O)$_2$-R_9,

-C(O)-CH_2-O-R_9,

-C(O)C(O)-R_{10},

-R_9,

-H, and

-C(O)C(O)-OR_{10};

X_5 is $\underset{|}{\text{-CH-}}$ or $\underset{|}{\text{-N-}}$;

Y_2 is H_2 or O;

X_7 is -N(R_8)- or -O-;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(H)-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$;
$-C(O)-CH_2N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9, -C(O)-R_9, -C(O)-N(H)-R_9, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a -C_{1-6} straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group consisting of -NH_2, -CO_2H, -Cl, -F, -Br, -I, -NO_2, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, -OR_5, -NHR_5, OR_9, -NHR_9, R_9, -C(O)-R_{10}, and

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 O
/ \
   CH2,
\ /
 O
```

provided that when -Ar_3 is substituted with a Q_1 group which comprises one or more additional -Ar_3 groups, said additional -Ar_3 groups are not substituted with another -Ar_3.

Preferably, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

Alternatively, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$.

More preferably:

m is 1;

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

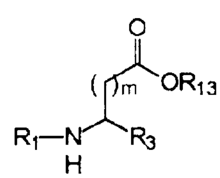
each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

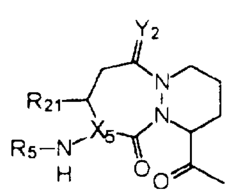
The ICE inhibitors of another embodiment (C) of this invention are those of formula (II):

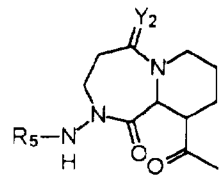
(II) 

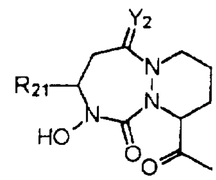
wherein:

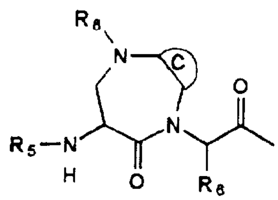
m is 1 or 2;

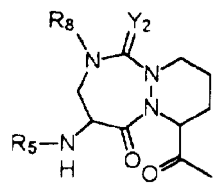
R_1 is selected from the group consisting of the following formulae:

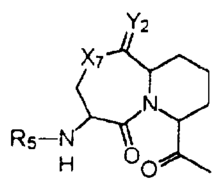
(e10)  ;

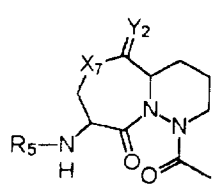
(e11)  ;

(e12)  ;

(w2)  ;

(y1)  ;

(y2)  ;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is selected from the group consisting of:

$-CN$,

$-C(O)-H$,

$-C(O)-CH_2-T_1-R_{11}$,

$-C(O)-CH_2-F$,

$-C=N-O-R_9$, and

$-CO-Ar_2$;

R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$$-C(O)-N\begin{array}{l} \diagup R_{10} \\ \diagdown R_{10}, \end{array}$$

$-S(O)_2-R_9$,

$-C(O)-CH_2-O-R_9$,

$-C(O)C(O)-R_{10}$,

$-R_9$,

$-H$, and

$-C(O)C(O)-OR_{10}$,

X_5 is $-\underset{|}{C}H-$ or $-\underset{|}{N}-$;

Y_2 is H_2 or O;

X_7 is $-N(R_8)-$ or $-O-$;

each T_1 is independently selected from the group consisting of $-O-$, $-S-$, $-S(O)-$, and $-S(O)_2-$;

R_6 is selected from the group consisting of $-H$ and $-CH_3$;

R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

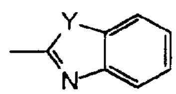
$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and
$-C(O)-Ar_4$;

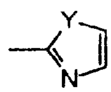
R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

$-OR_{13}$ is optionally -N(H)-OH;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and

15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group consisting of -NH_2, -CO_2H, -Cl, -F, -Br, -I, -NO_2, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, -OR_5, -NHR_5, OR_9, -NHR_9, R_9, -C(O)-R_{10}, and

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 O
/ \
   CH2;
\ /
 O
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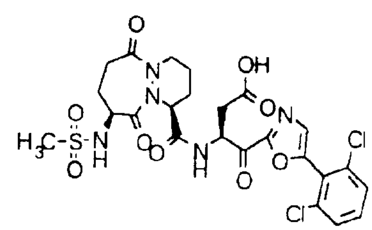
provided that when -Ar_3 is substituted with a Q_1 group which comprises one or more additional -Ar_3 with another -Ar_3.

Preferred compounds of this embodiment include, but are not limited to:

220b



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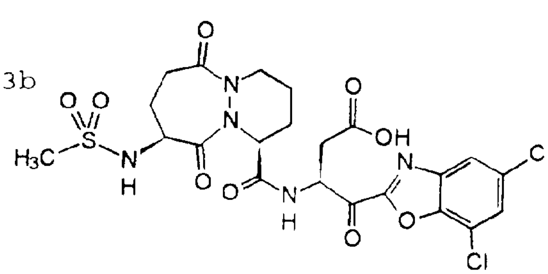

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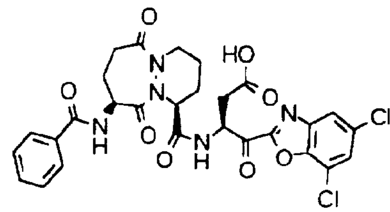

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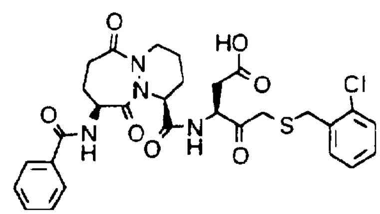

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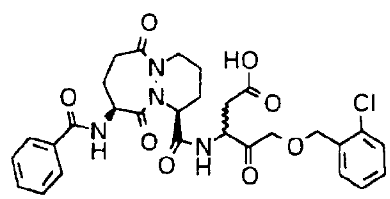

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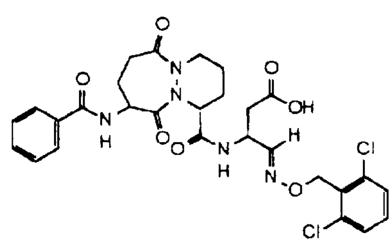

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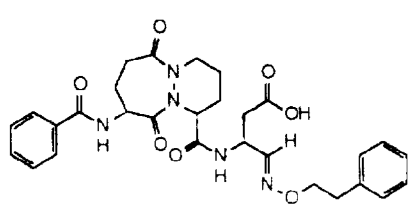

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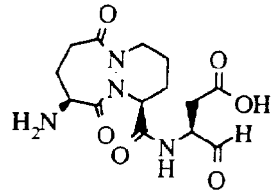

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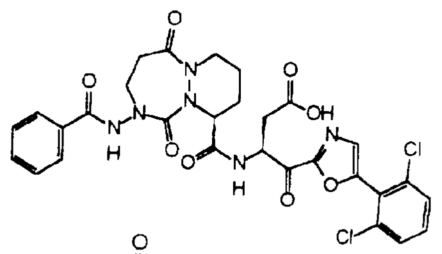

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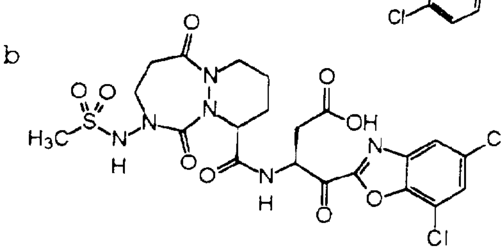

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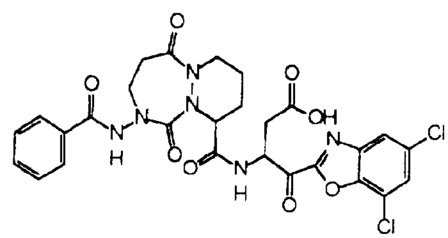

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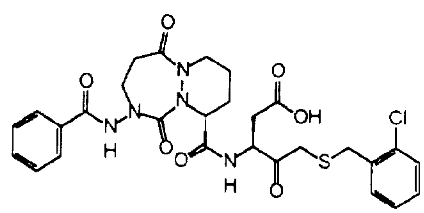

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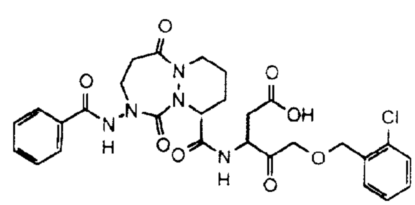

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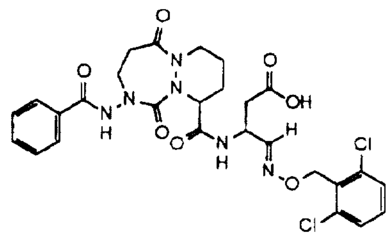

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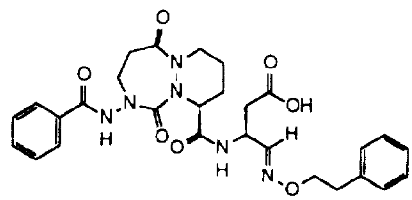

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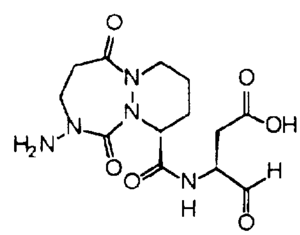

Preferred compounds of embodiment C employ formula (II), wherein R_1 is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment C employ formula (II), wherein R_1 is (e12) and the other substituents are as defined above.

Other preferred compounds of embodiment C employ formula (II) wherein R_1 is (y1) and the other substituents are as defined above.

Other preferred compounds of embodiment C employ formula (II) wherein R_1 is (y2) and the other substituents are as defined above.

Other preferred compounds of embodiment C of employ formula (II) wherein R_1 is (z) and the other substituents are as defined above.

Other preferred compound of embodiment C employ formula (II) wherein R_1 is (w2) and the other substituents are as defined above.

More preferably, R_1 is (w2) and

m is 1;

ring C is benzo, pyrido, or thieno;

R_3 is selected from the group consisting of -C(O)-H, -C(O)-Ar_2, and -C(O)CH_2-T_1-R_{11};

R_5 is selected from the group consisting of:
-C(O)-R_{10}, wherein R_{10} is -Ar_3;
-C(O)O-R_9, wherein R_9 is -CH_2-Ar_3;
-C(O)C(O)-R_{10}, wherein R_{10} is -CH_2Ar_3;
-R_9, wherein R_9 is a C_{1-2} alkyl group substituted with -Ar_3; and
-C(O)C(O)-OR_{10}, wherein R_{10} is -CH_2Ar_3;

T_1 is O or S;

R_6 is H;

R_8 is selected from the group consisting -C(O)-R_{10}, -C(O)-CH_2-OR_{10}, and -C(O)CH_2-N(R_{10})(R_{10}), wherein R_{10} is H, CH_3, or -CH_2CH_3;

R_{11} is selected from the group consisting of -Ar_4, -$(CH_2)_{1-3}$-Ar_4, and -C(O)-Ar_4;

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

Ar_2 is (hh);

Y is O;

Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl;

Ar_4 is phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

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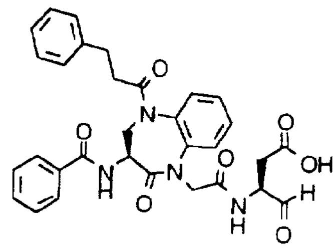
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferred compounds of this embodiment include, but are not limited to:

605a



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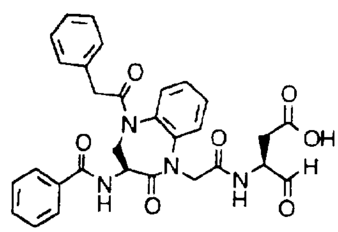

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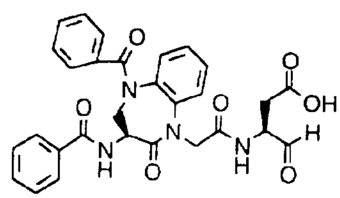

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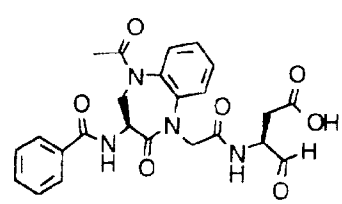

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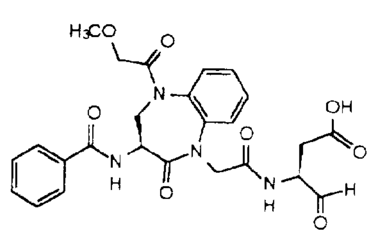

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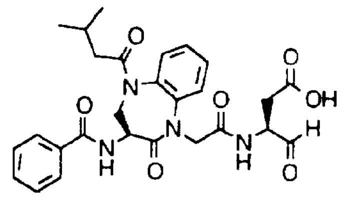

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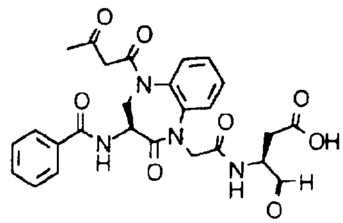

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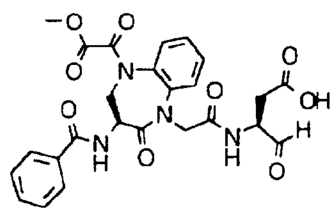

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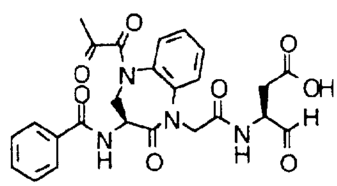

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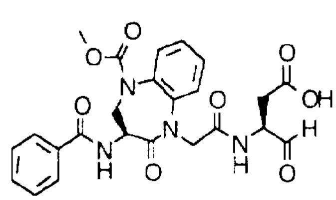

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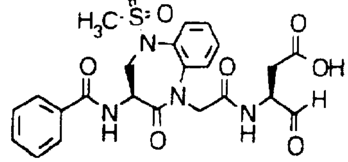

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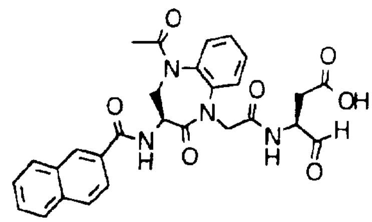

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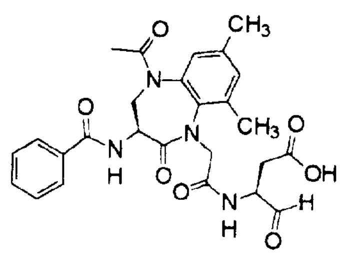

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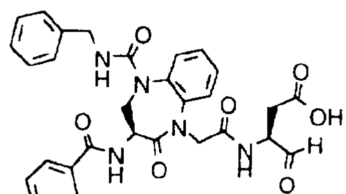

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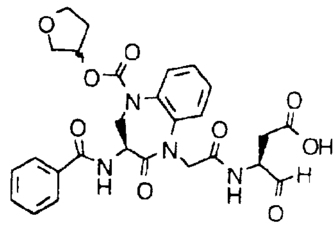

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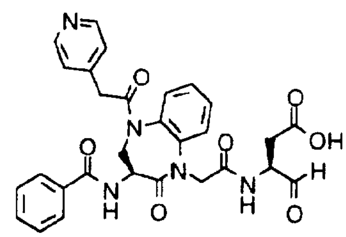

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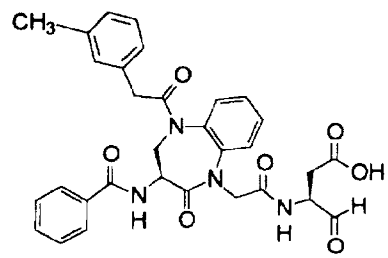

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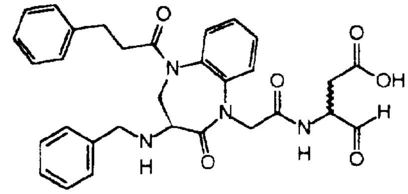

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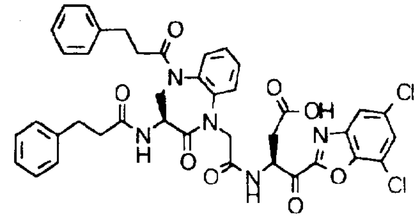

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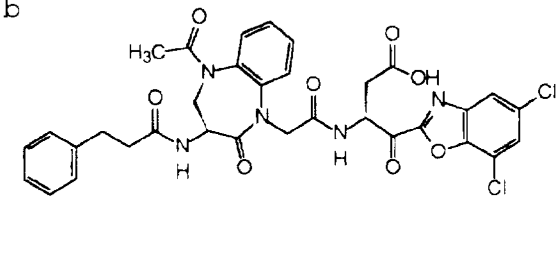

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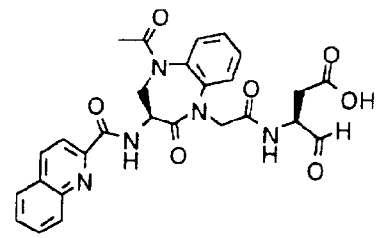

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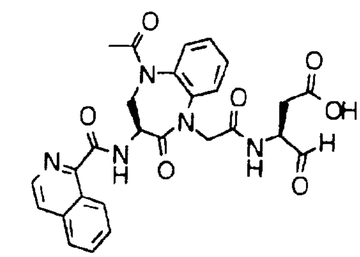

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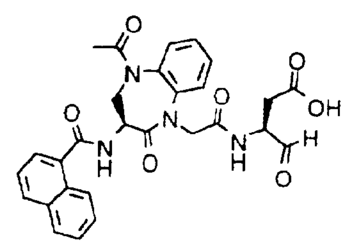

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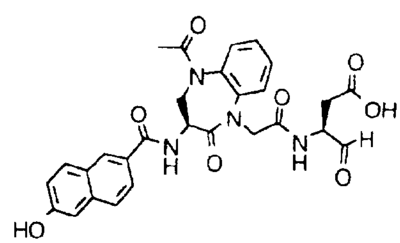

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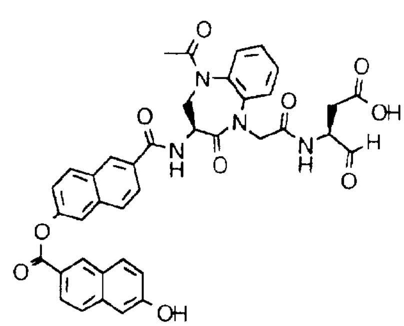

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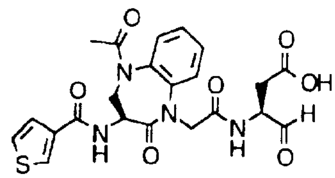

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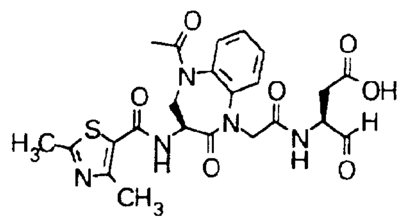

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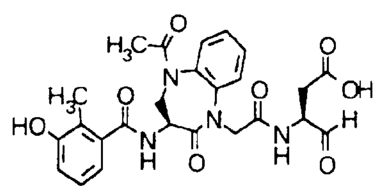

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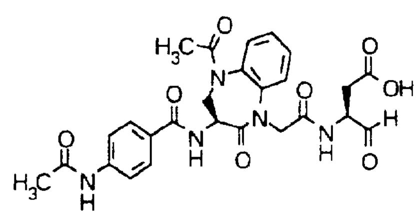

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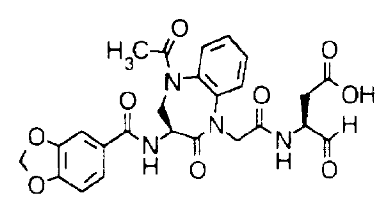
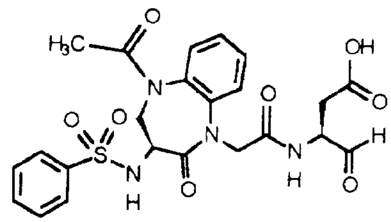
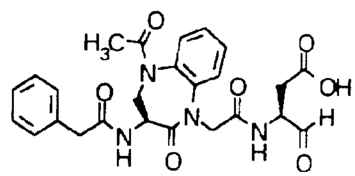
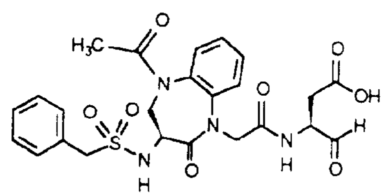
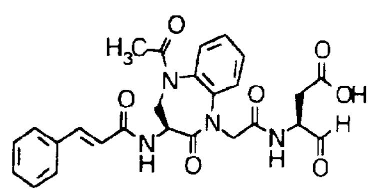
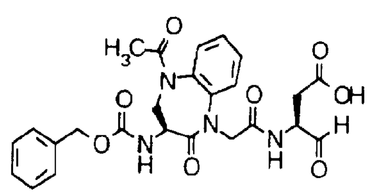


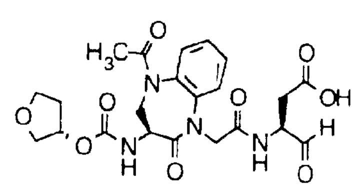
629 

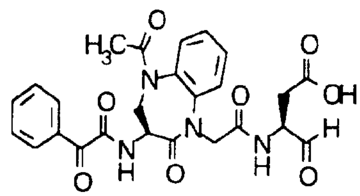
630 

631 

632 

633 

634 

635 

Other preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10), X_5 is CH, and the other substituents are as defined above.

More preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10), X_5 is CH, R_3 is $CO-Ar_2$, and the other substituents are as defined above.

Other more preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10), X_5 is CH, R_3 is $-C(O)-CH_2-T_1-R_{11}$, R_{11} is $-(CH_2)_{1-3}-Ar_4$, and the other substituents are as defined above.

Other more preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10) and X_5 is CH and

R_3 is $-C(O)-CH_2-T_1-R_{11}$;
T_1 is O; and
R_{11} is $-C(O)-Ar_4$,

and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$, and
$-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds,

m is 1;

T_1 is O or S;

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

Ar_2 is (hh);

Y is O, and

Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

Ar_4 is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

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     CH2,
  \ /
   O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other more preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10), X_5 is CH, R_3 is -C(O)-H, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,
$-R_9$, and
$-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds,

m is 1;

T_1 is O or S;

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

Ar_2 is (hh);

Y is O, and

Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

Ar_4 is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

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 O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$,

Other more preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10) and X_5 is CH, R_3 is $-CO-CH_2-T_1-R_{11}$, and R_{11} is $-Ar_4$, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,
$-C(O)-C(O)-R_{10}$,
$-R_9$, and
$-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds,

m is 1;

T_1 is O or S;

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

Ar_2 is (hh);

Y is O, and

Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

Ar_4 is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

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 O
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   CH2,
\ /
 O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10), X_5 is N, and the other substituents are as defined above.

More preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $CO-Ar_2$, and the other substituents are as defined above.

Other more preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $-C(O)-CH_2-T_1-R_{11}$, R_{11} is $-(CH_2)_{1-3}-Ar_4$, and the other substituents are as defined above.

Other more preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10) and X_5 is N and:

R_3 is $-C(O)-CH_2-T_1-R_{11}$;

T_1 is O; and

R_{11} is $-C(O)-Ar_4$, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$.

m is 1;

T_1 is O or S;

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

Ar_2 is (hh);

Y is O, and

Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

Ar_4 is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

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   O
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     CH2,
  \ /
   O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other more preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is -C(O)-H, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9, and

-C(O)-NH-R_{10}.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

-$S(O)_2$-R_9,

-$S(O)_2$-NH-R_{10},

-C(O)-C(O)-R_{10},

-R_9, and

-C(O)-C(O)-OR_{10}.

Most preferably, in these more preferred compounds,

m is 1;

T_1 is O or S;

R_{13} is H or a -C_{1-4} straight or branched alkyl group optionally substituted with -Ar_3, -OH, -OR_9, or -CO_2H, wherein the R_9 is a -C_{1-4} branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or -CH_3;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl, optionally substituted by -Q_1;

Ar_2 is (hh);

Y is O, and

Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

Ar_4 is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

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  O
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    CH2,
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  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other more preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $-CO-CH_2-T_1-R_{11}$, R_{11} is $-Ar_4$, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds

m is 1;

T_1 is O or S;

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

Ar_2 is (hh);

Y is O, and

Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

Ar_4 is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

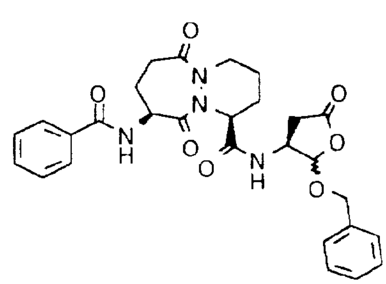
each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
  O
 / \
    CH2,
 \ /
  O
```

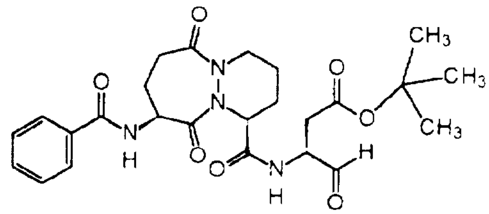
wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferred compounds of embodiment B include, but are not limited to:

213e 

302



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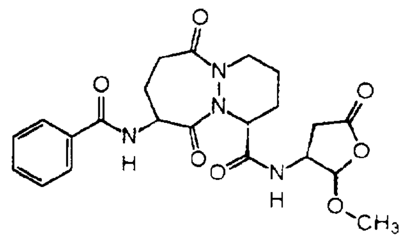
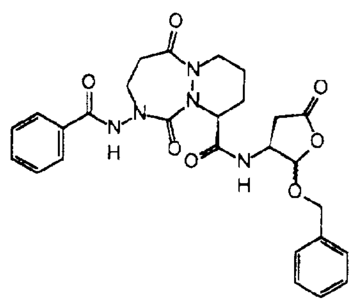


813e



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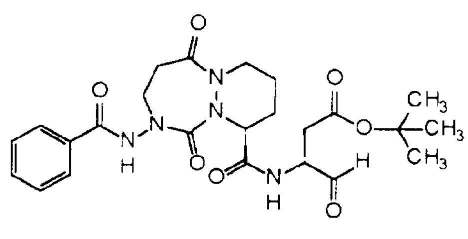
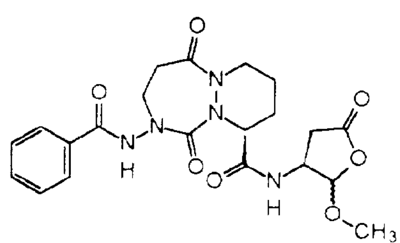
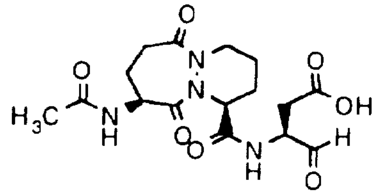


904a



Preferred compounds of embodiment C include, but are not limited to:

214c



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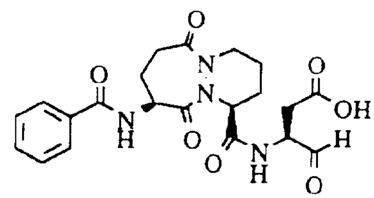

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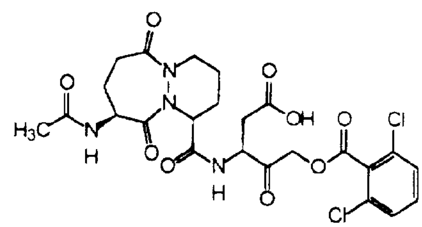

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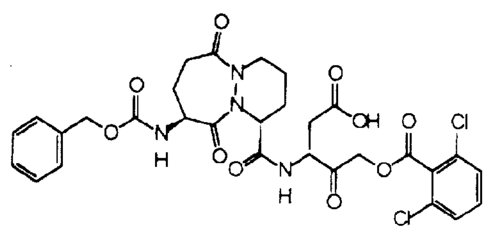

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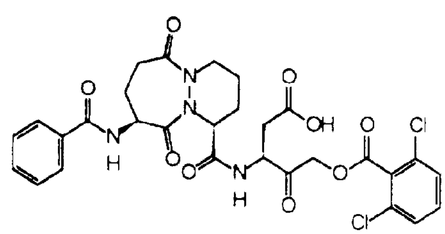

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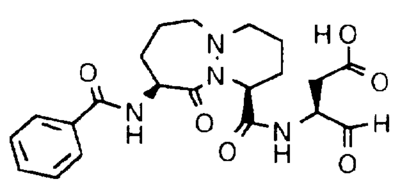

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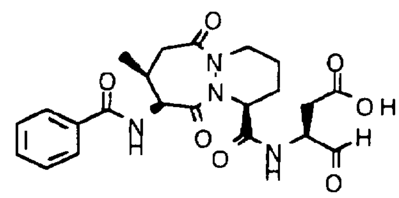

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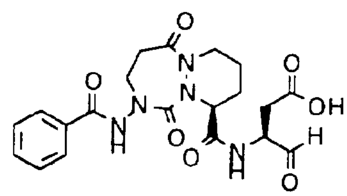

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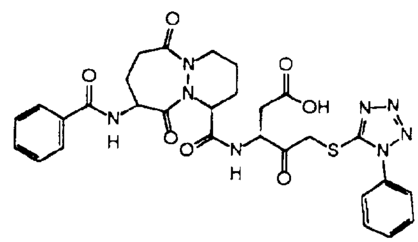

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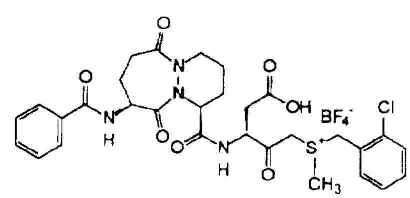

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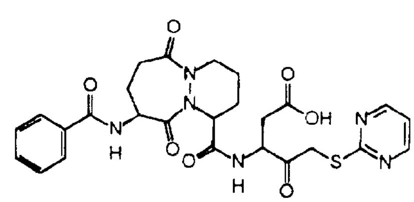

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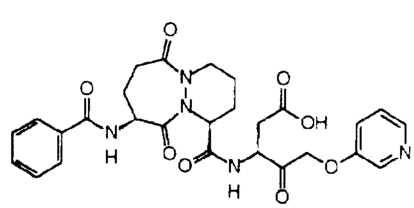

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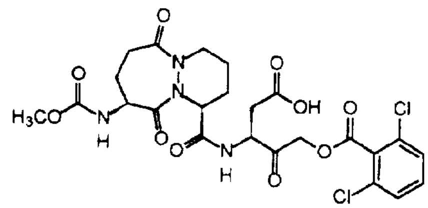

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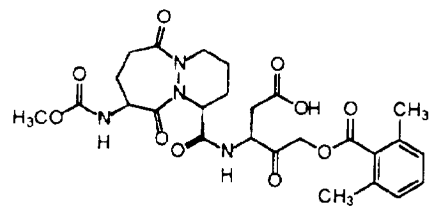

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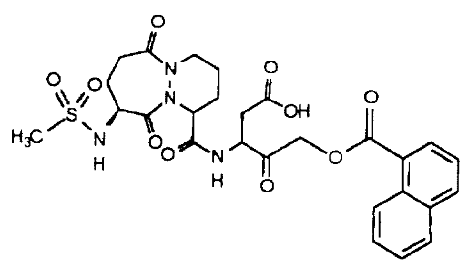

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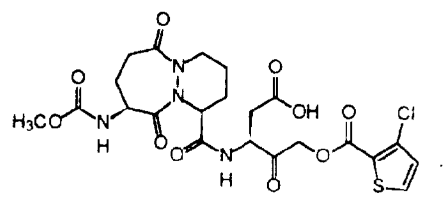

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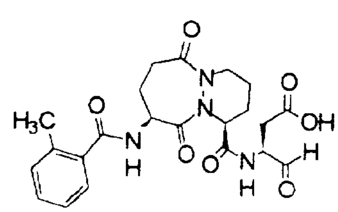

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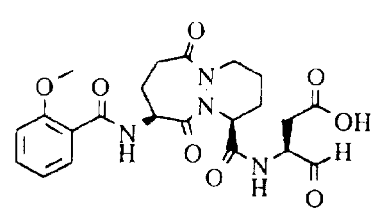

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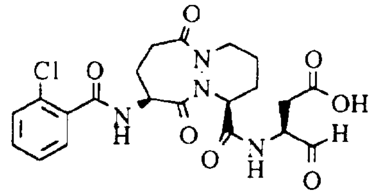

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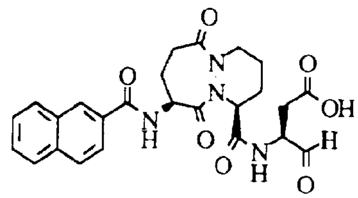

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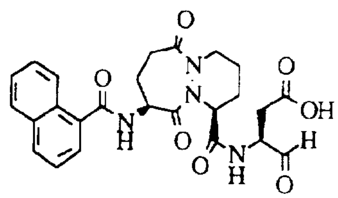

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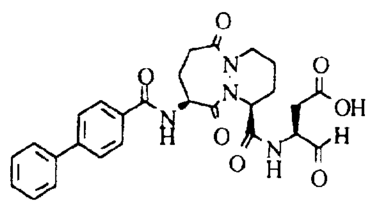

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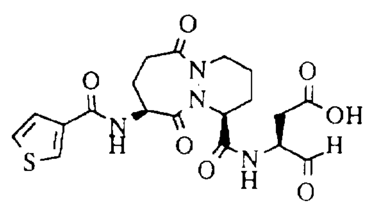

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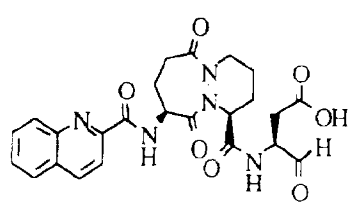

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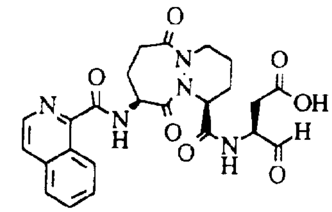

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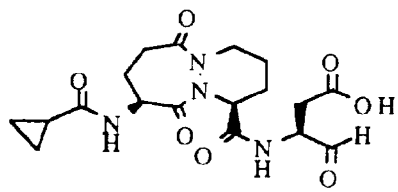

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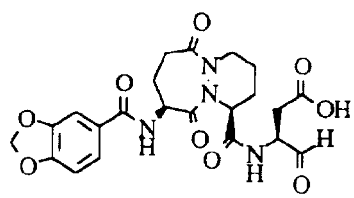

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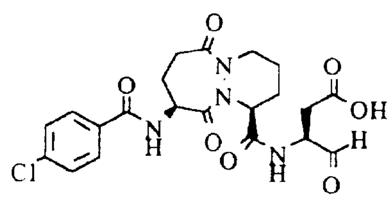

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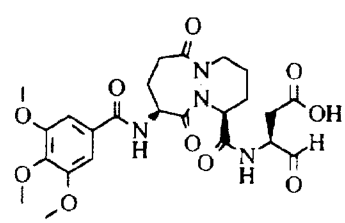

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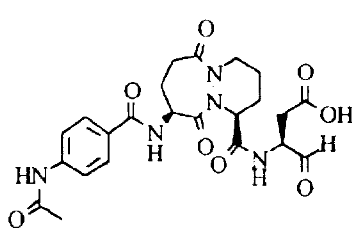

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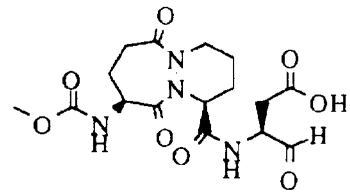

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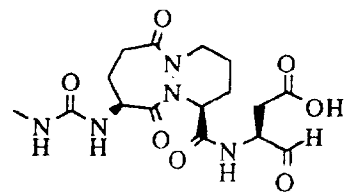

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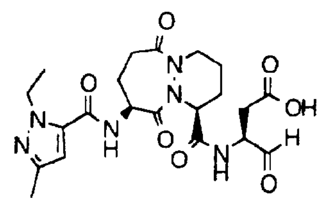

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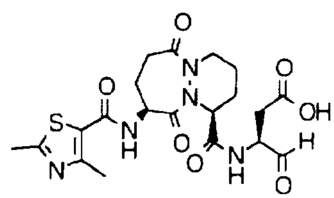

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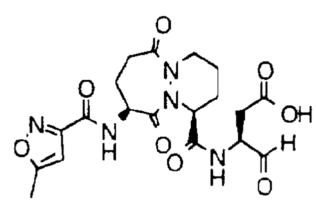

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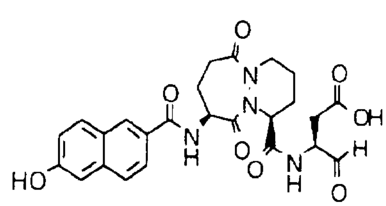

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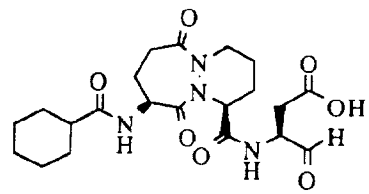

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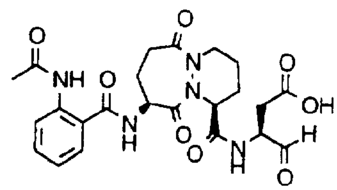

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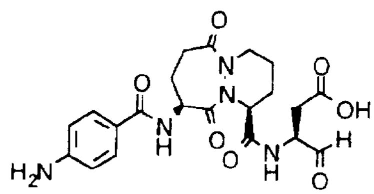

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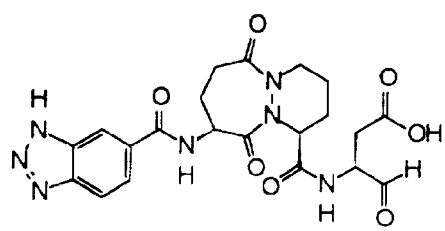

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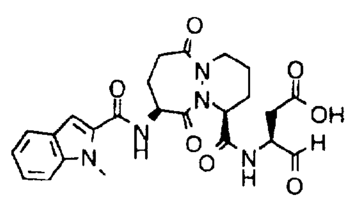

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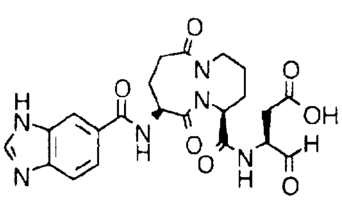

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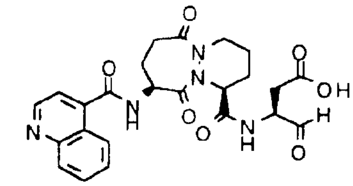

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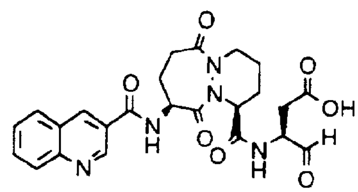

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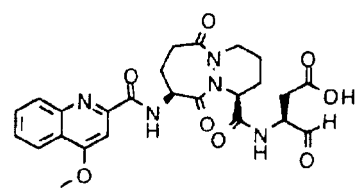

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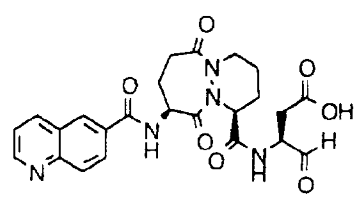

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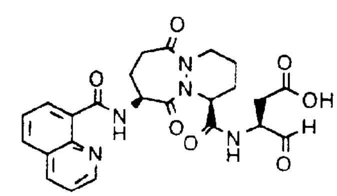

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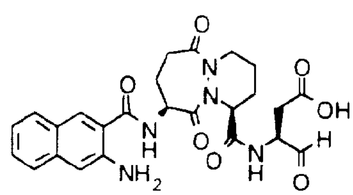

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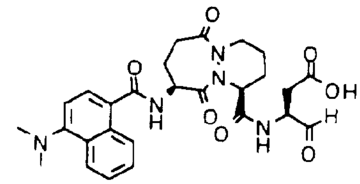

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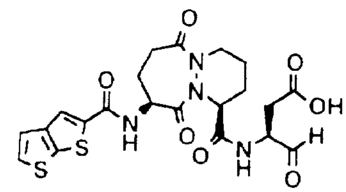

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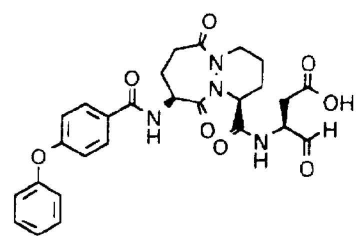

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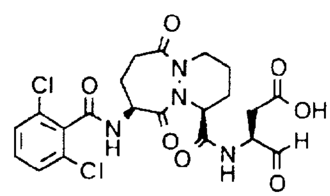

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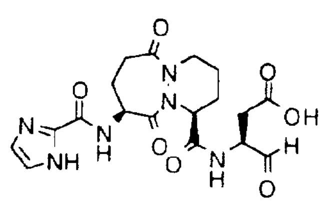

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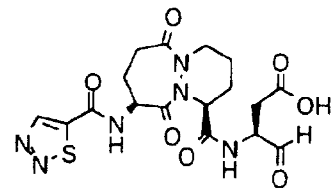

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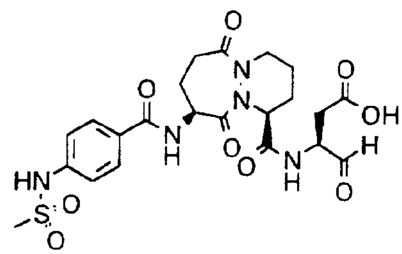

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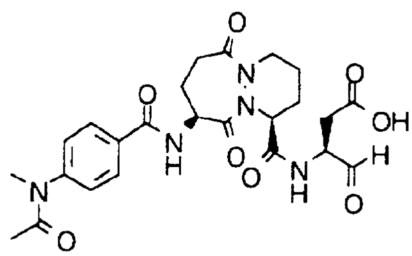

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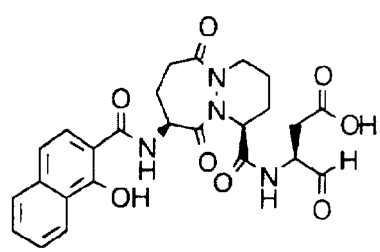

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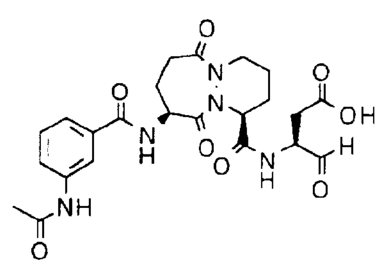

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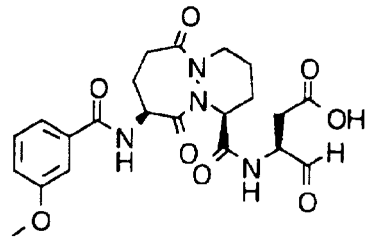

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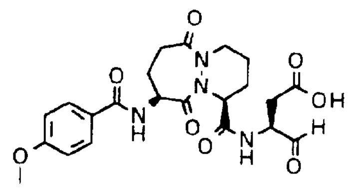

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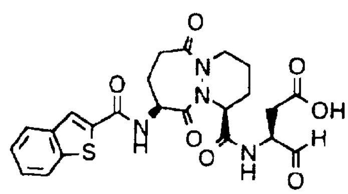

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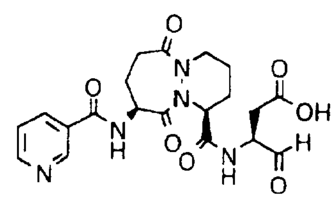

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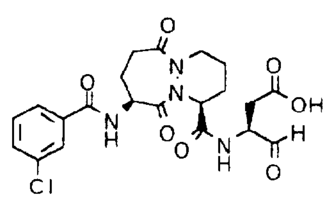

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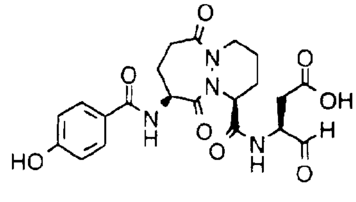

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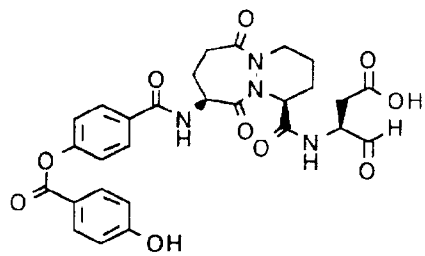

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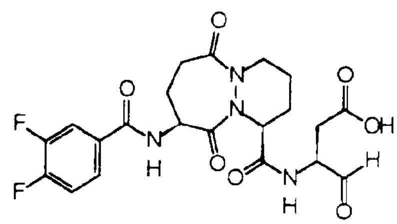

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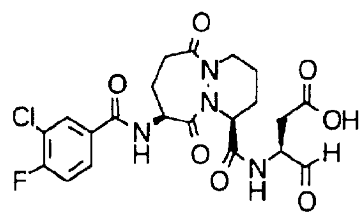

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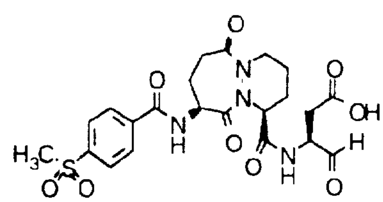

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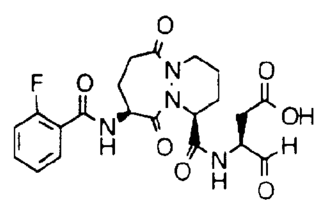

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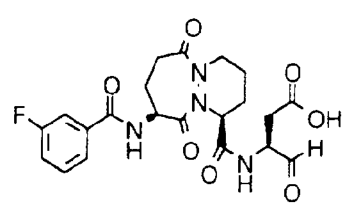

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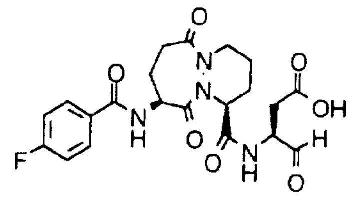

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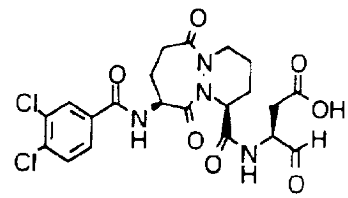

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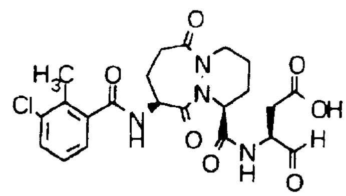

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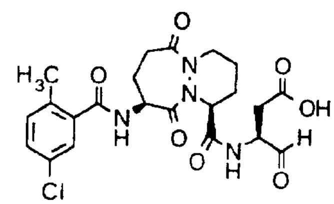

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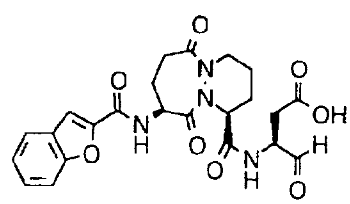

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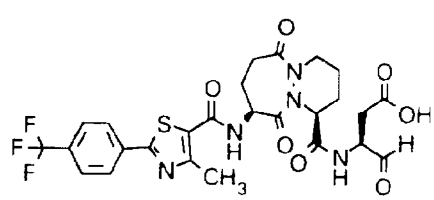

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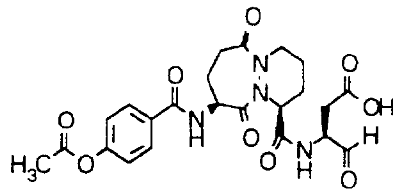

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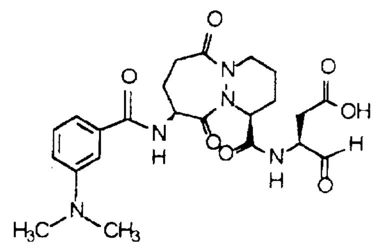

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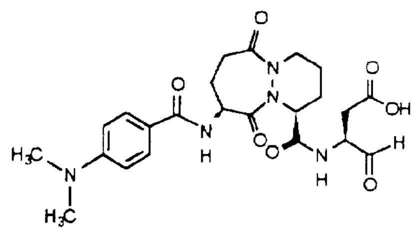

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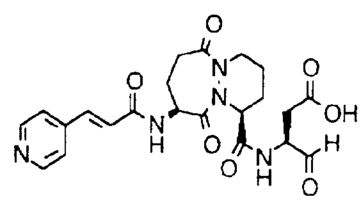

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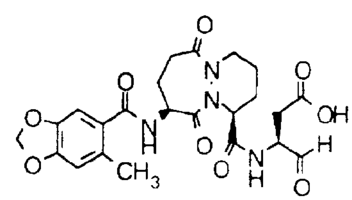

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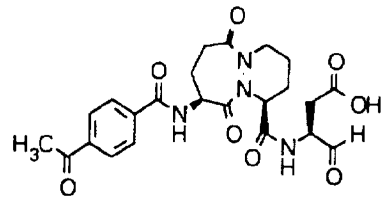

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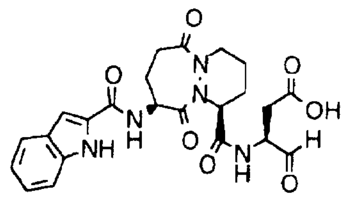

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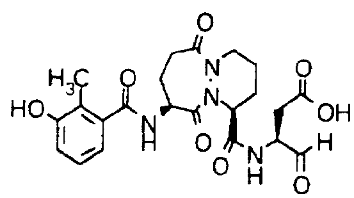

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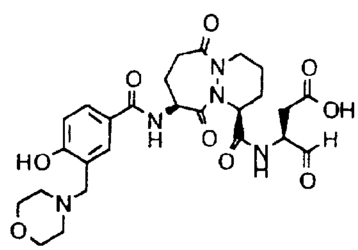

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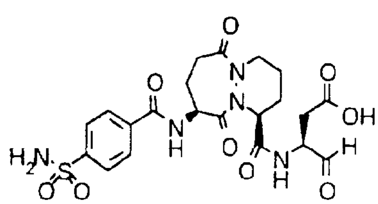

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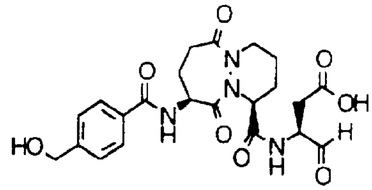

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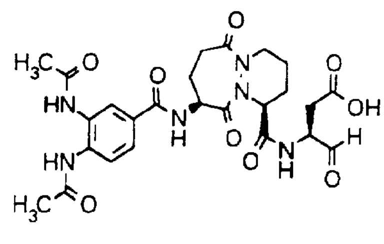

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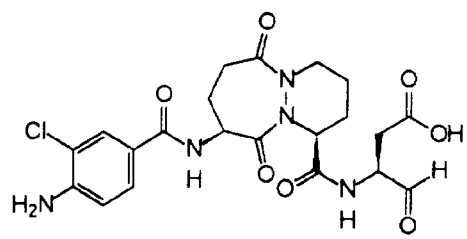

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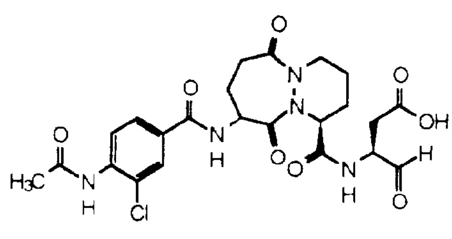

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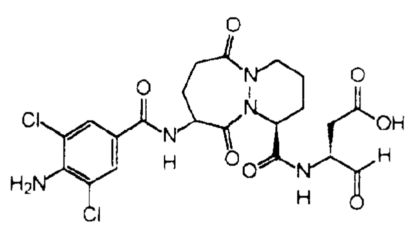

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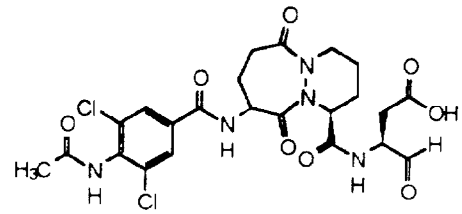

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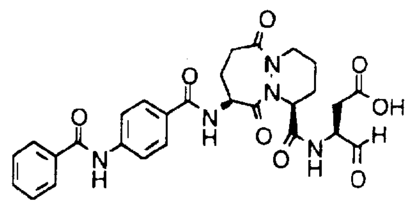

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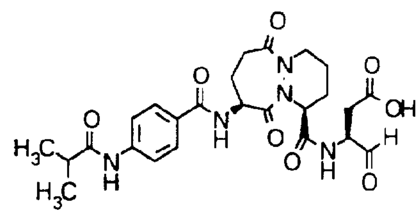

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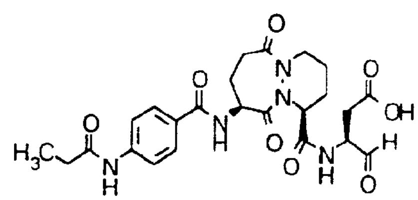

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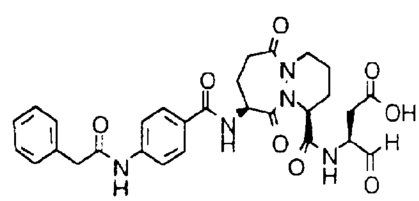

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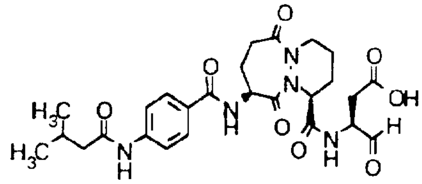

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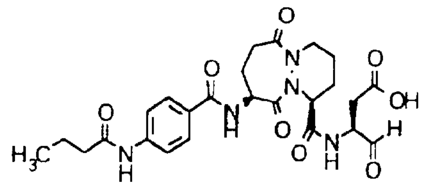

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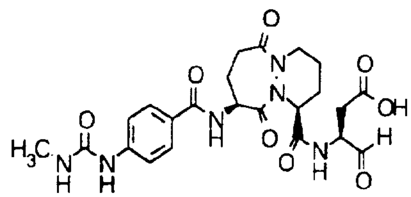

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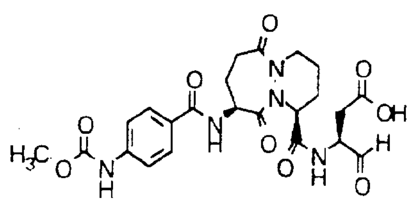

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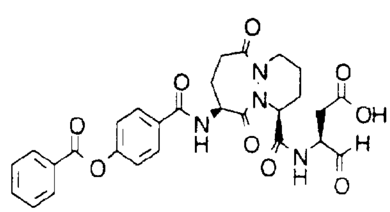

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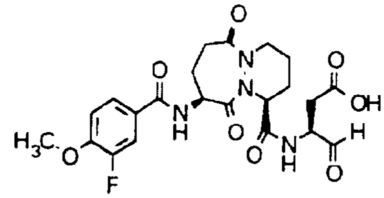

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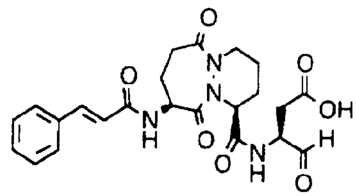

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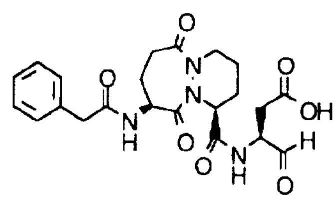

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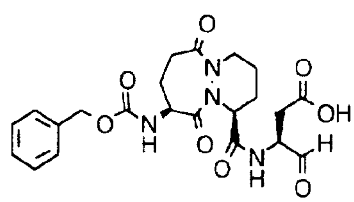

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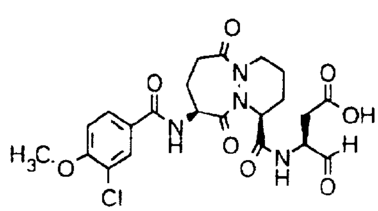

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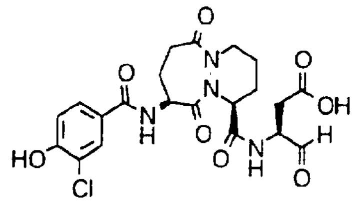

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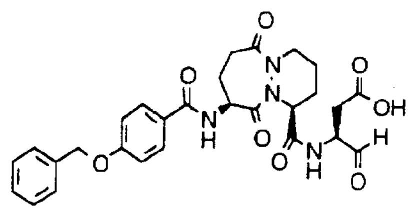

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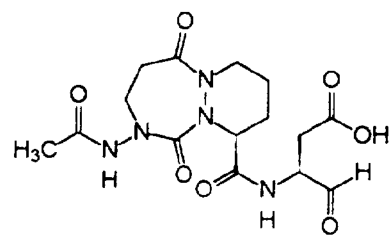

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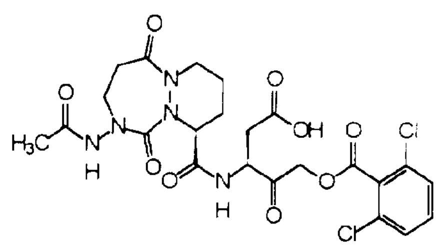

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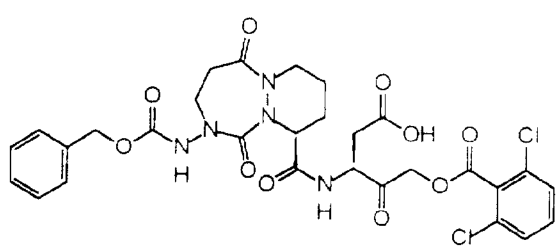

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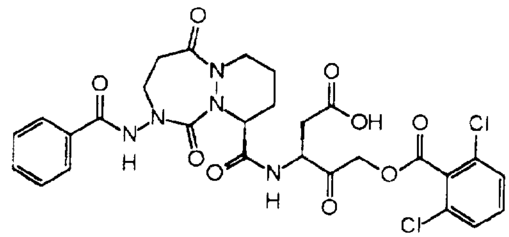

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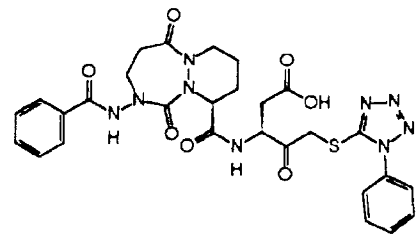

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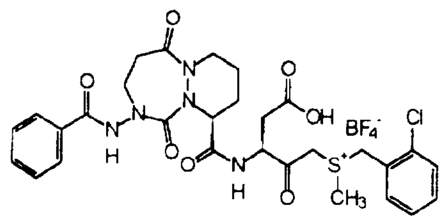

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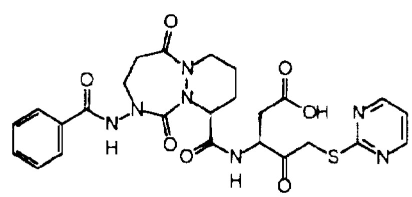

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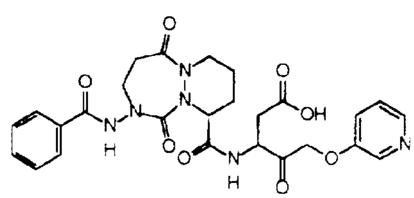

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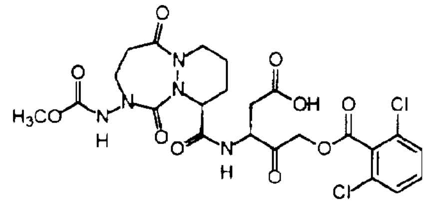

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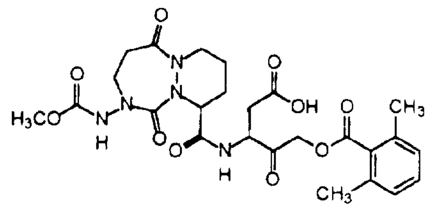

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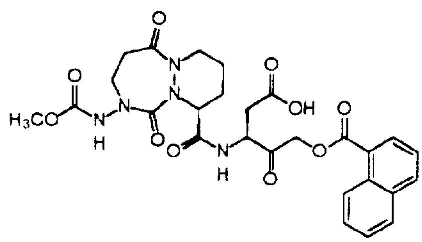

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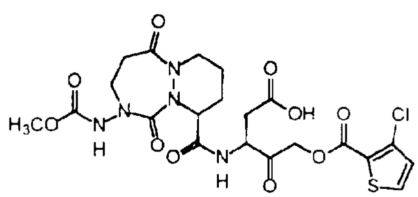

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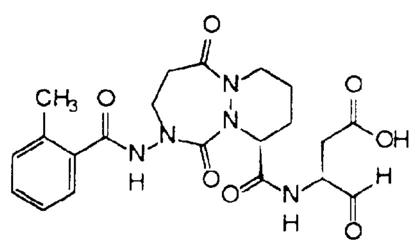

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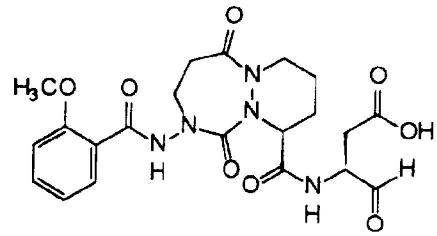

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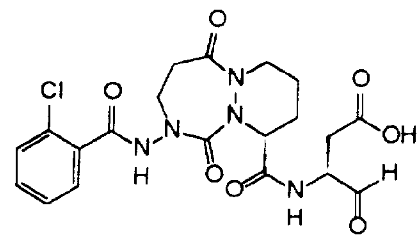

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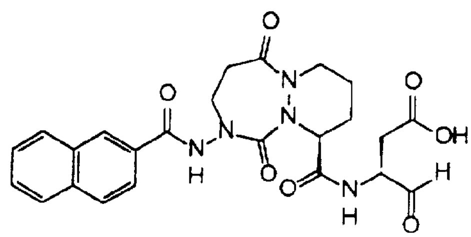

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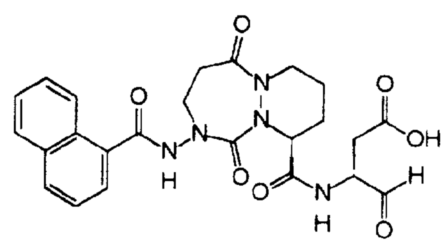

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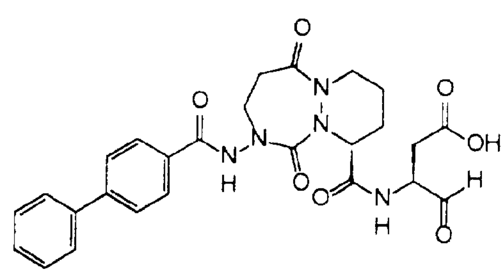

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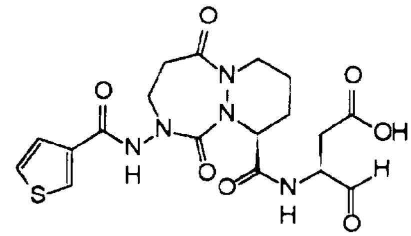

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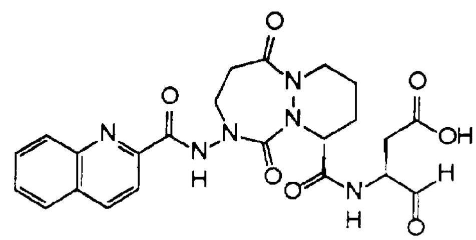

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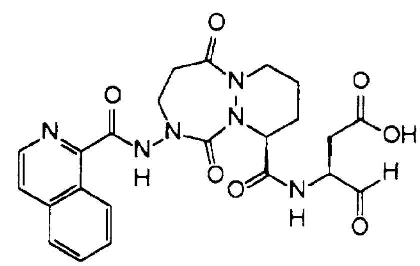

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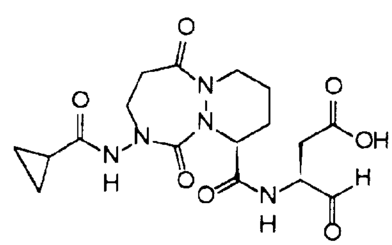

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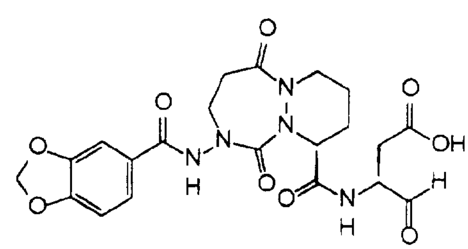

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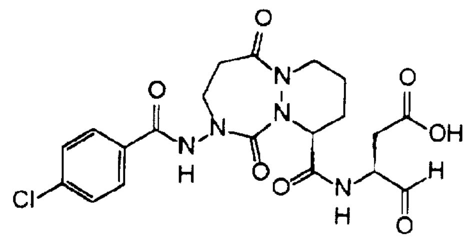

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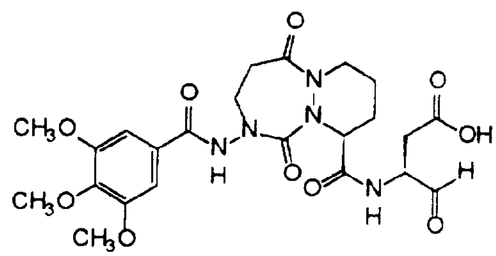

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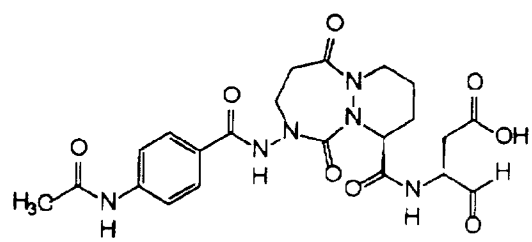

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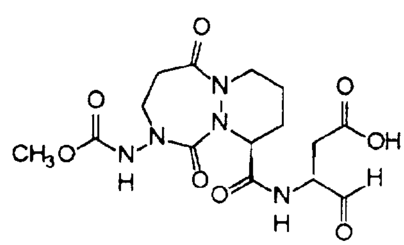

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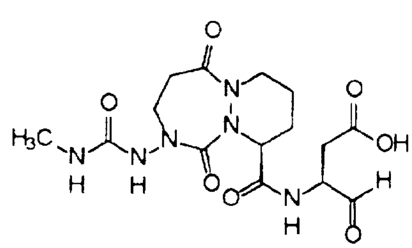

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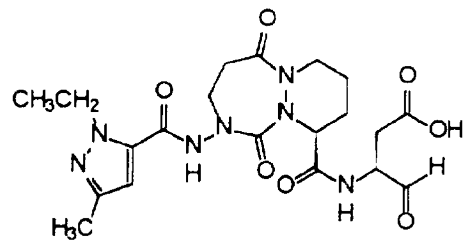

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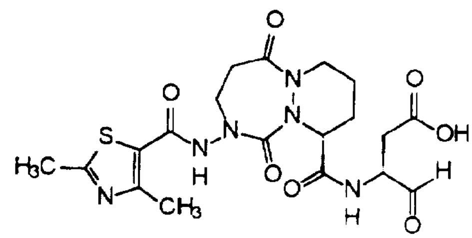

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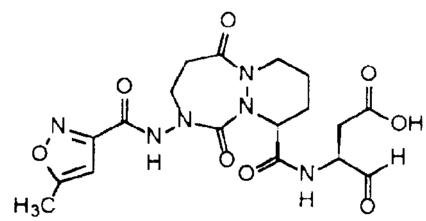

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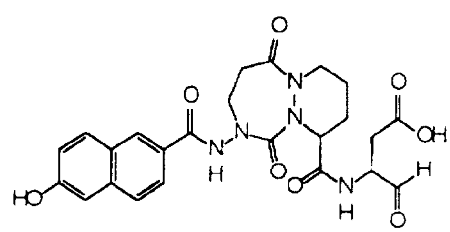

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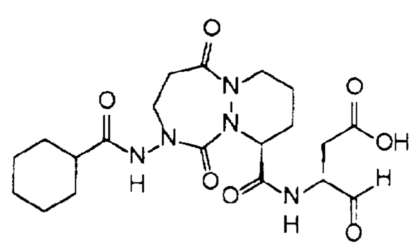

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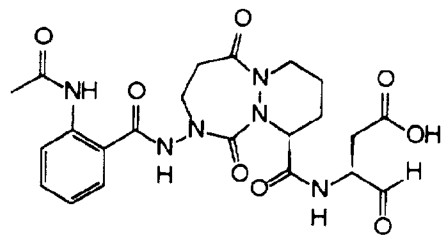

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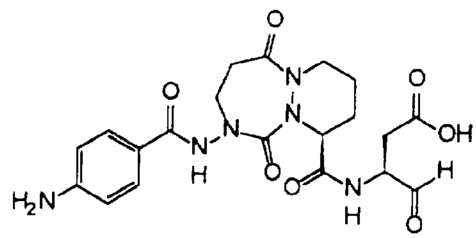

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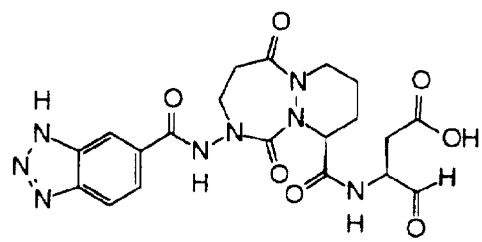

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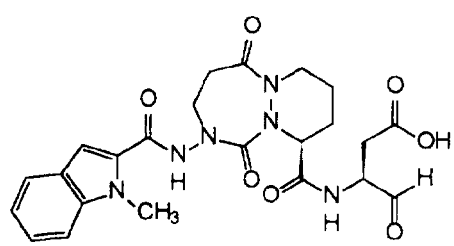

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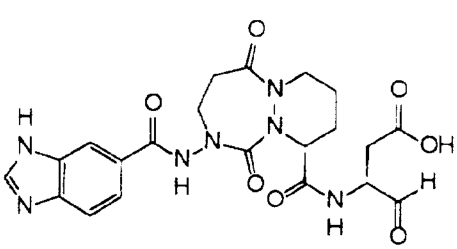

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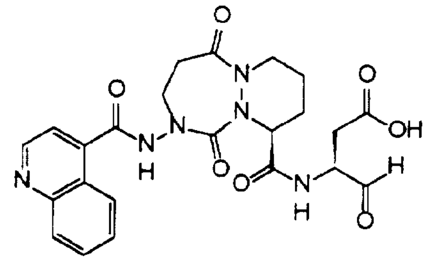

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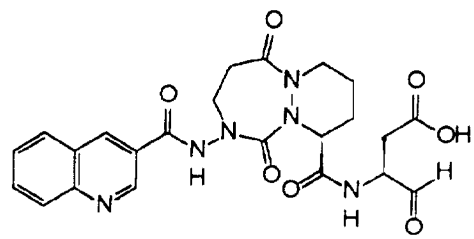

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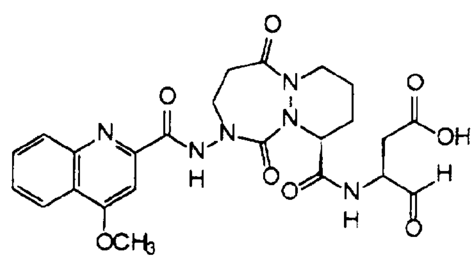

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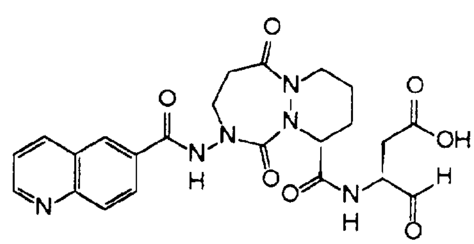

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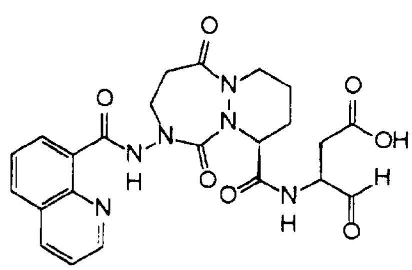

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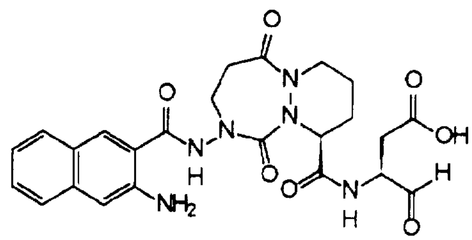

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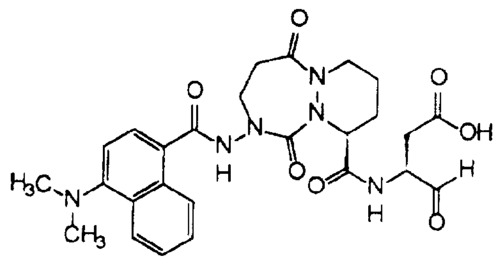

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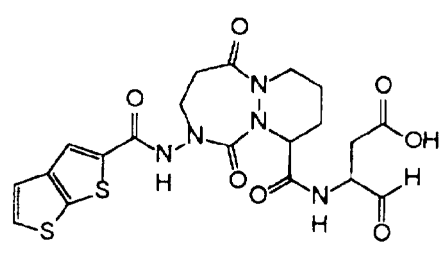

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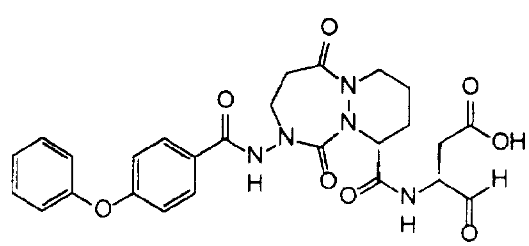

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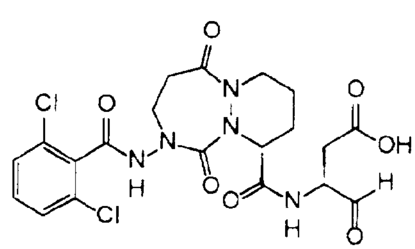

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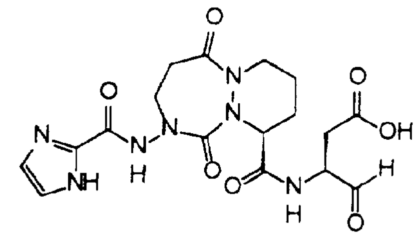

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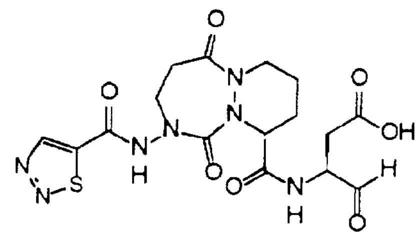

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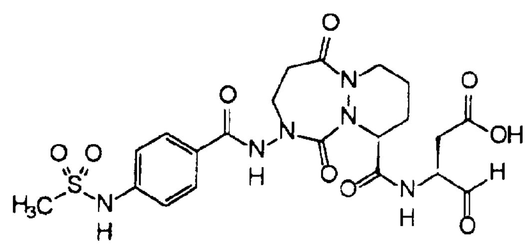

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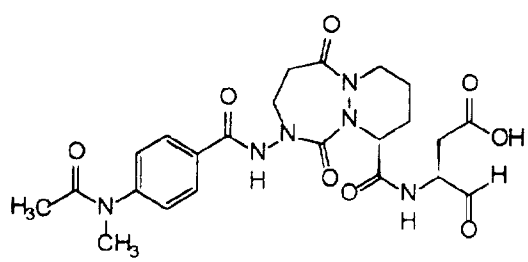

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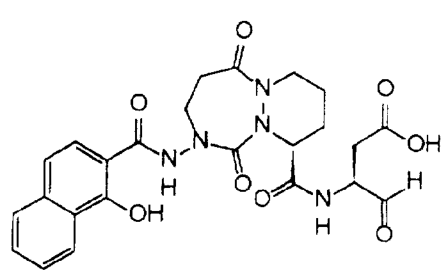

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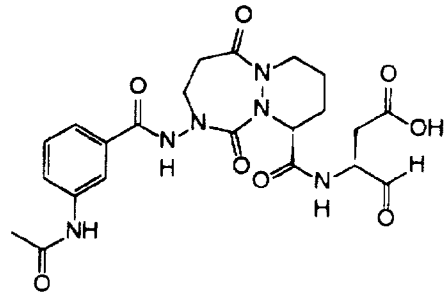

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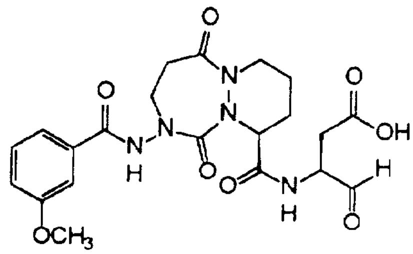

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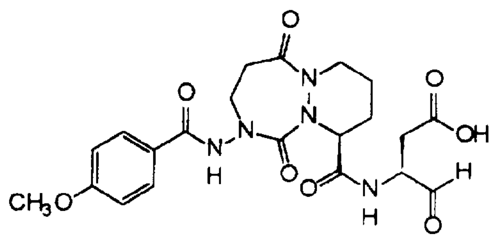

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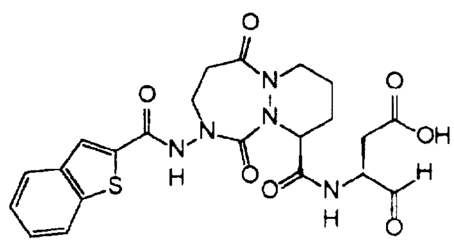

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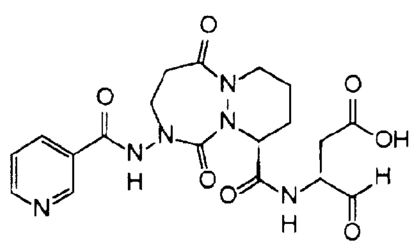

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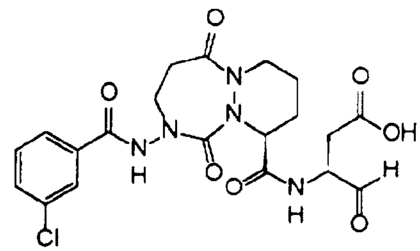

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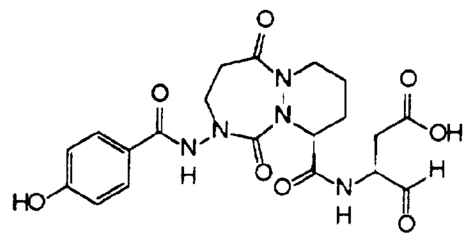

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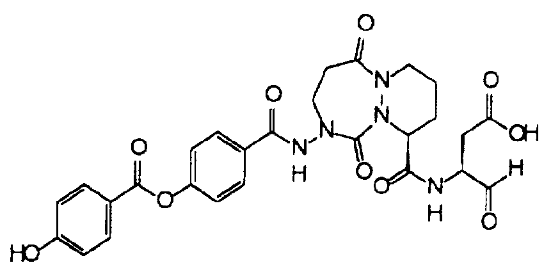

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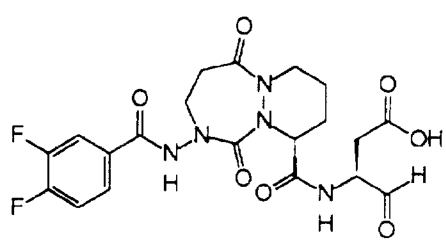

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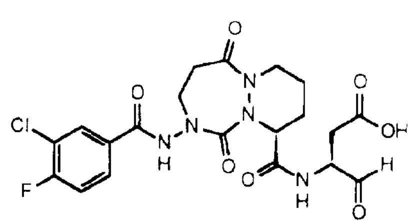

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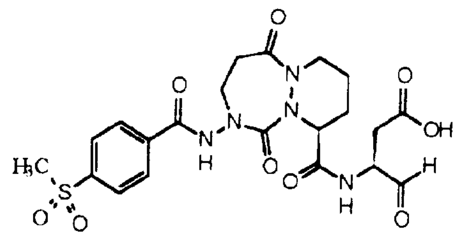

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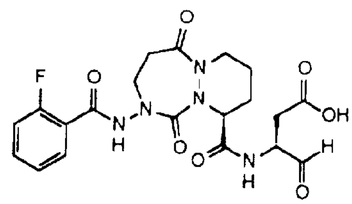

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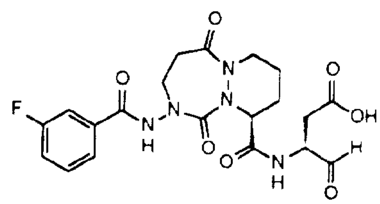

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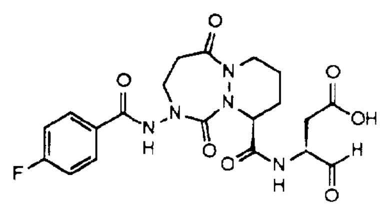

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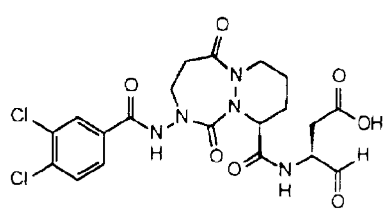

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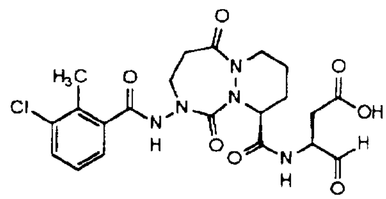

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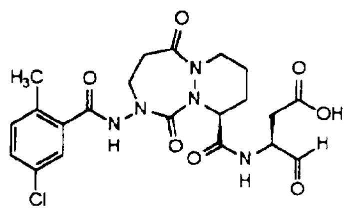

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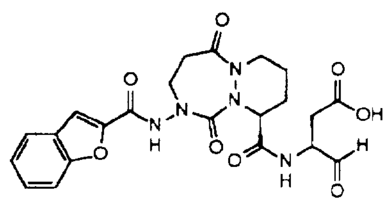

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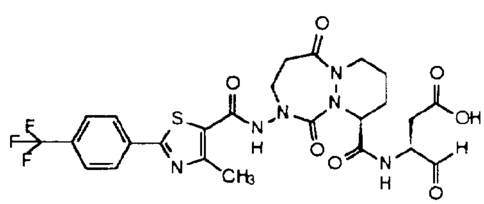

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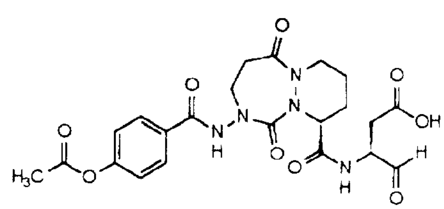

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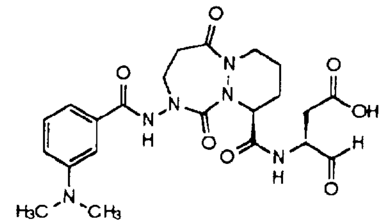

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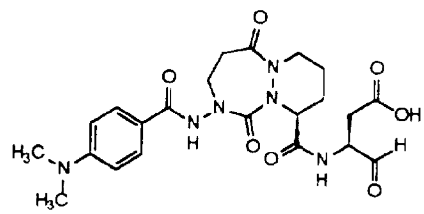

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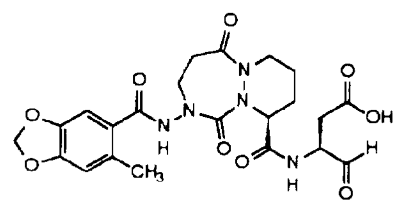

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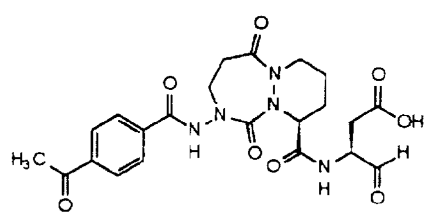

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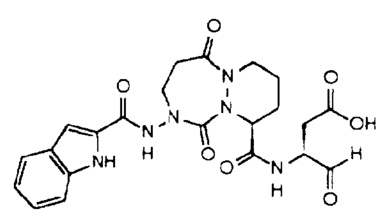

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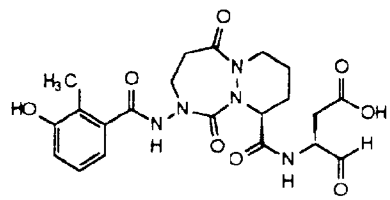

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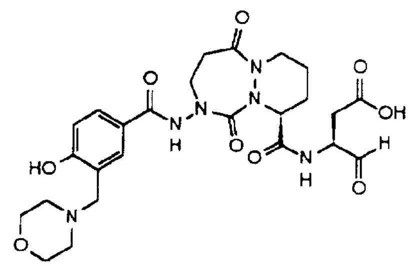

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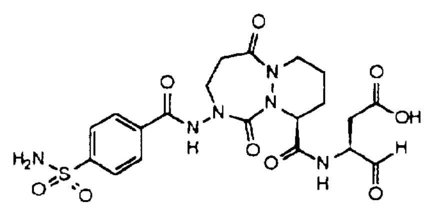

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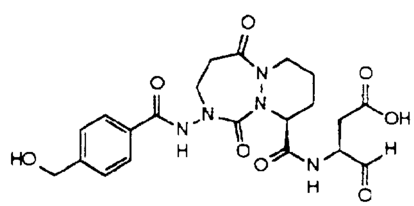

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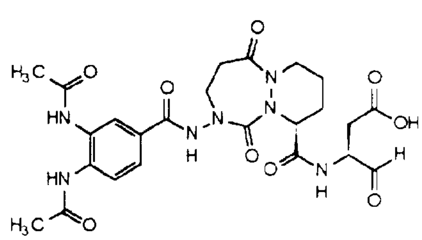

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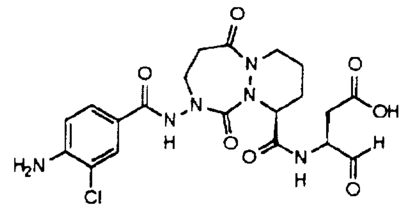

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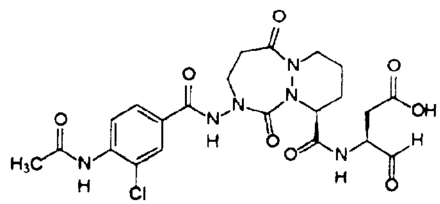

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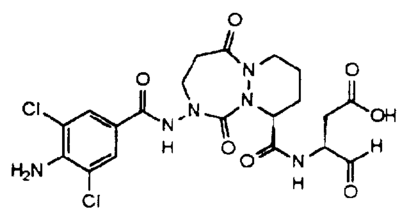

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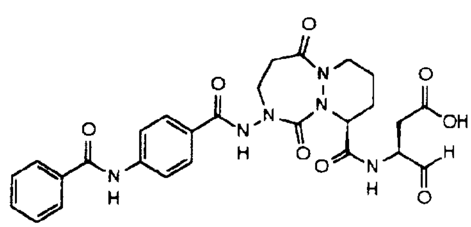

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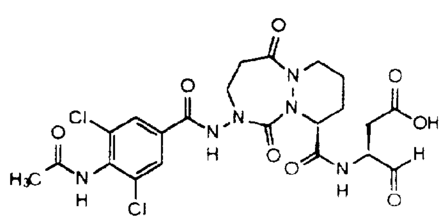

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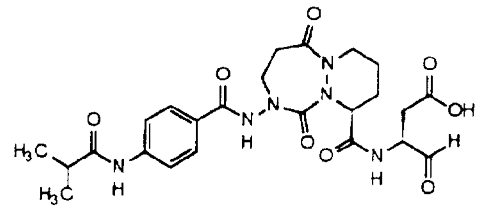

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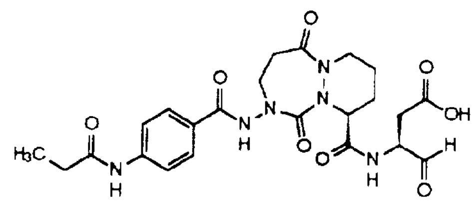

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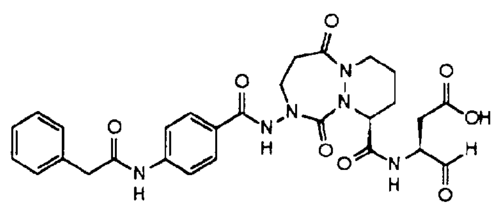

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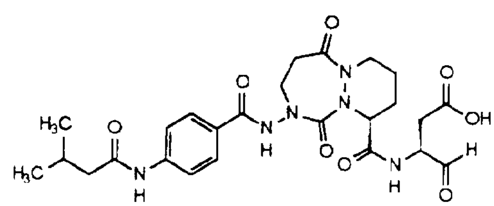

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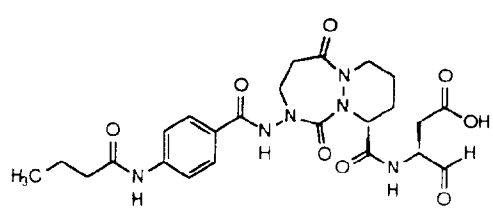

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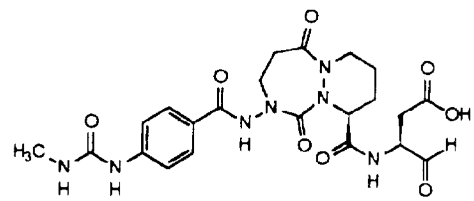

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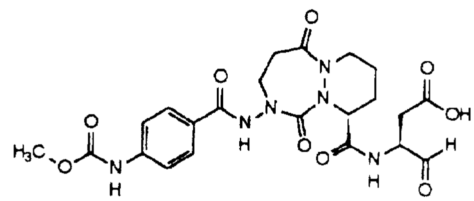

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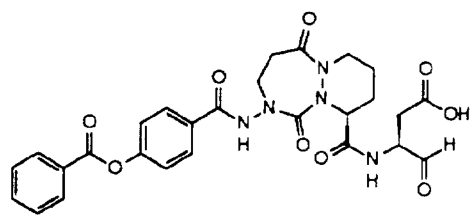

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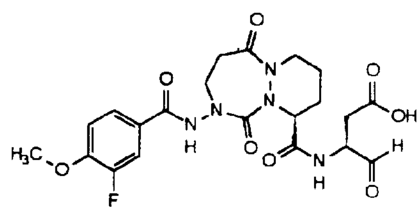

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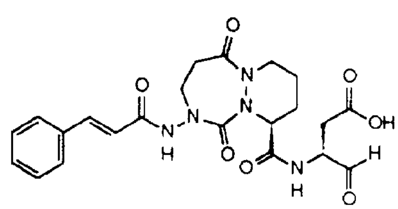

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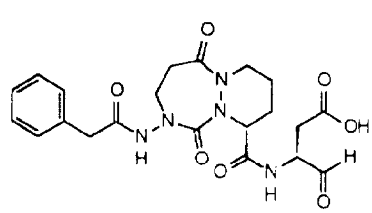

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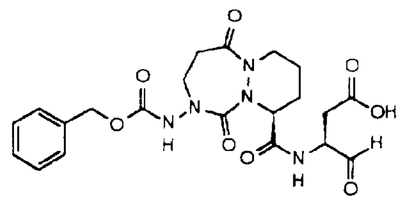

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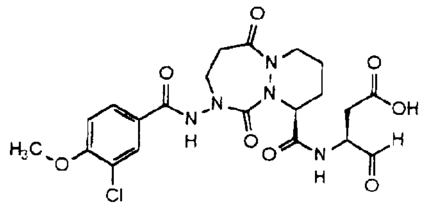

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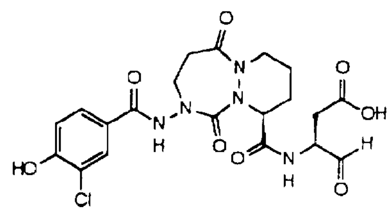

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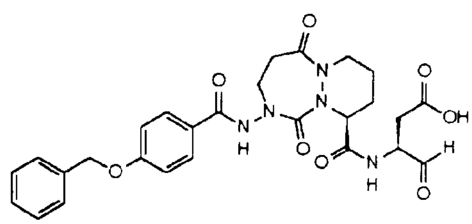

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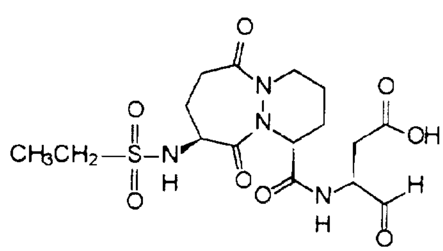

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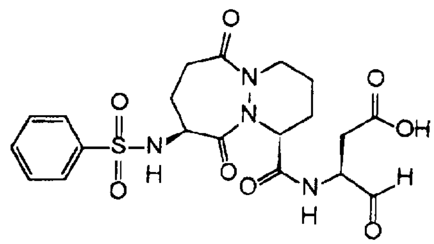

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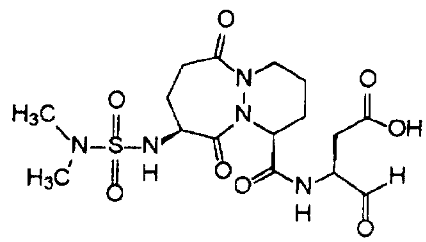

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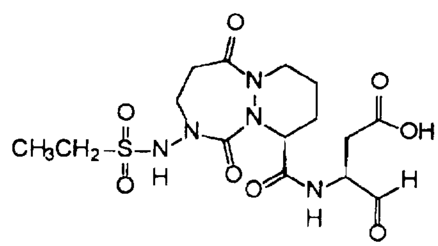

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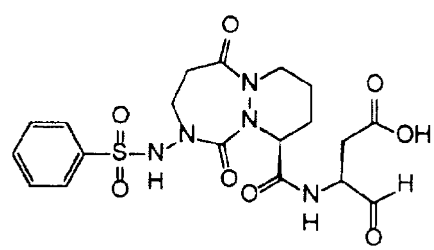

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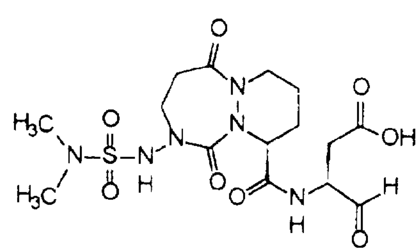

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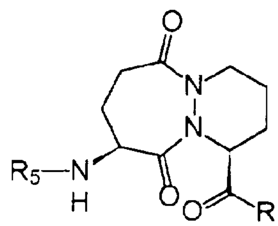
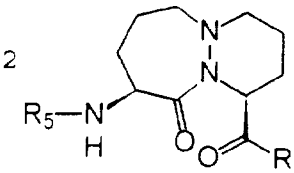
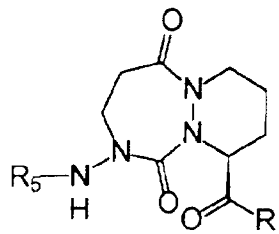
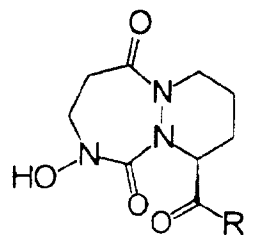
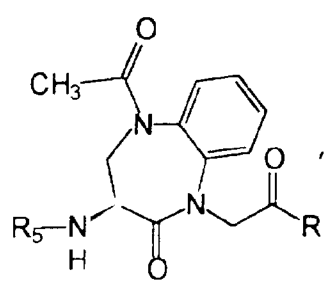
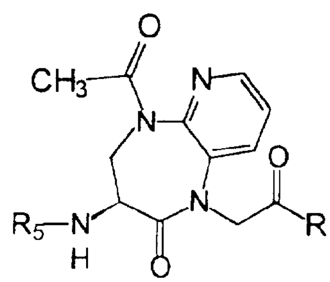
1  ,

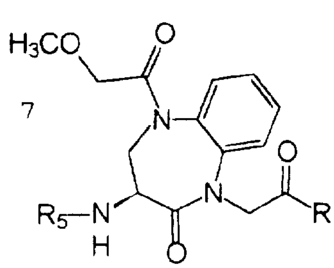
2  ,

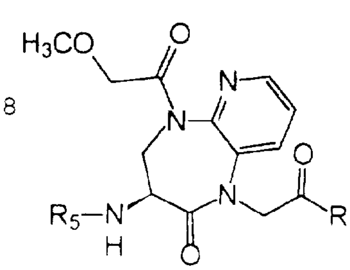
3  ,

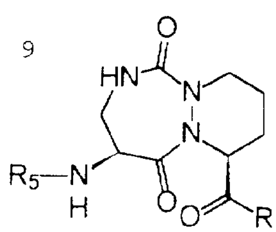
4  ,

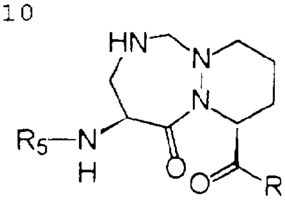
5  ,

6  ,

7  ,

8  ,

9  ,

10  ,

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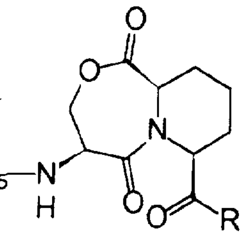
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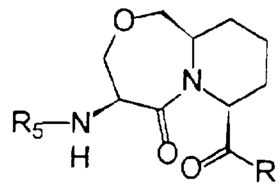
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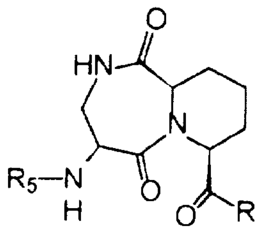
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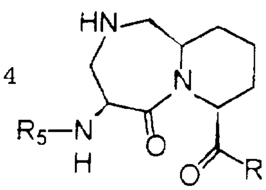
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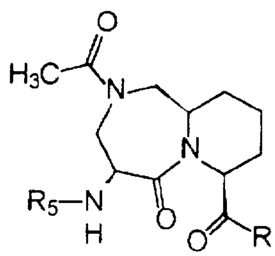
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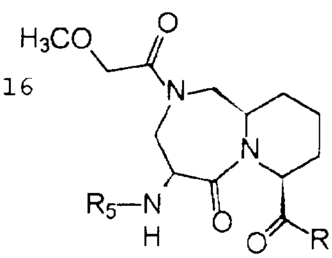
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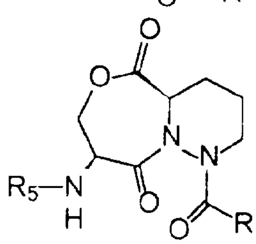
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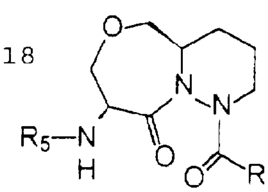
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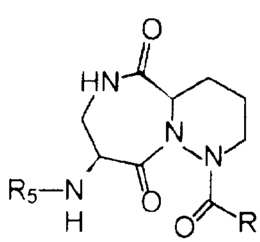
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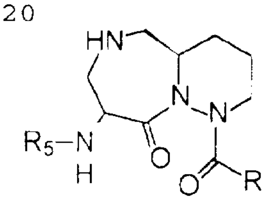
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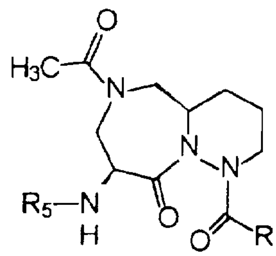
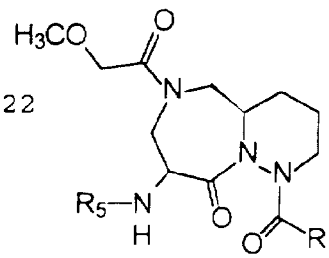
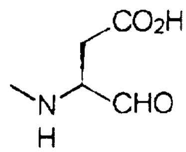
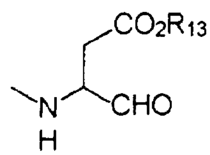
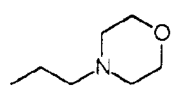
21  , 22  , .

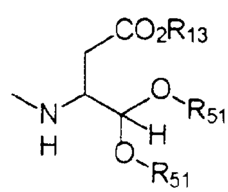
wherein:

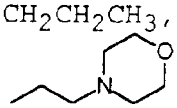
R is  ,

 , wherein

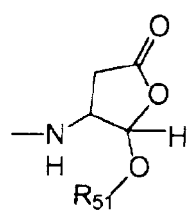
R_{13} is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)(CH_3)$, $-CH_2CH_2CH_2CH_3$, $-CH_2-CH(CH_3)CH_3$, $-C(CH_3)_3$, $-CH_2Ph$, or

 ,

 , wherein

R_{13} is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)(CH_3)$, $-CH_2CH_2CH_2CH_3$, $-CH_2-CH(CH_3)CH_3$, $-C(CH_3)_3$, $-CH_2Ph$, or  , and

each R_{51} is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)(CH_3)$, $-CH_2CH_2CH_2CH_3$, $-CH_2-CH(CH_3)CH_3$, $-C(CH_3)_3$, $-CH_2Ph$, or taken together form a ethylenedioxy acetal or a propylenedioxy acetal; or



, wherein

R_{51} is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)(CH_3)$, $-CH_2CH_2CH_2CH_3$, $-CH_2-CH(CH_3)CH_3$, $-C(CH_3)_3$, $-CH_2Ph$, $-C(O)-CH_3$ or $-C(O)-Ph$;

R_5 in each of the above compounds is the same as any one of the R_5 moieties shown for any one of compounds 139, 214c, 214e, 404-413, 415-491, 493-501.

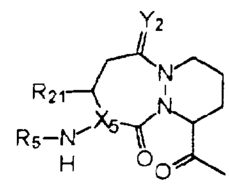
Specific compounds of this invention also include, but are not limited to, compounds comprising scaffolds 1-28, wherein R, R_{51}, and R_5 are as defined above, and in which the $-C(O)-$ of the R_5 moiety of any one of compounds 214c, 214e, 404-413, 415-418, 422-426, 430-456, 458-466, 468, 470-471, 473-491, 493, 495, 497-501 is replaced with $-CH_2-$, $-C(O)C(O)-$, or $-CH_2C(O)C(O)-$.

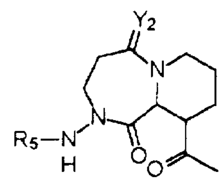
The ICE inhibitors of another embodiment (D) of this invention are those of formula (I):

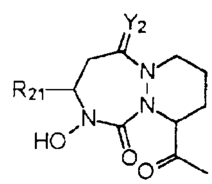
(I) $$R_1-\underset{\displaystyle H}{\underset{|}{N}}-R_2$$

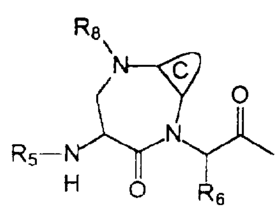
wherein:

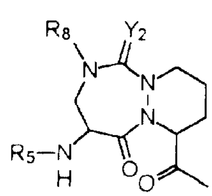
R_1 is selected from the group consisting of the following formulae:

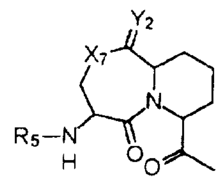
(e10)  ;

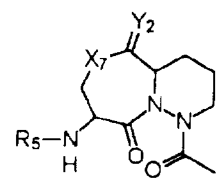
(e11)  ;

(e12)  ;

(w2)  ;

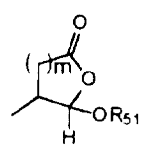
(y1)  ;

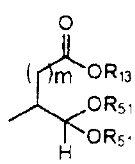
(y2)  ;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_2 is:

(a)  , or

(b)  ;

m is 1 or 2;

each R_5 is independently selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9,

-C(O)-N(R_{10})(R_{10})

-S(O)$_2$-R_9,

$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

X_5 is $-\underset{|}{C}H-$ or $-\underset{|}{N}-$;

Y_2 is H_2 or O;

X_7 is $-N(R_8)-$ or $-O-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(H)-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$;
$-C(O)-CH_2N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein

the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9, $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group

consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, OR_9, $-N(R_9)(R_{10})$, R_9, $-C(O)-R_{10}$, and

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  O
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    CH2,
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  O
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provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferably, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$, and
$-C(O)-NH-R_{10}$.

Alternatively, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-C(O)-R_{10}$,
$-R_9$, and
$-C(O)-C(O)-OR_{10}$.

More preferably:

m is 1;

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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    CH2,
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  O
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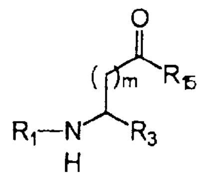
wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

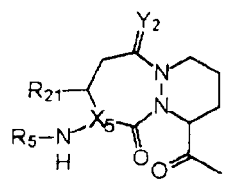
The ICE inhibitors of another embodiment (E) of this invention are those of formula (II):

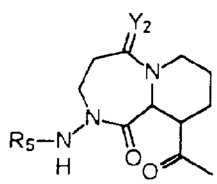
(II) 

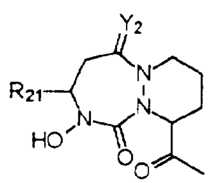
wherein:

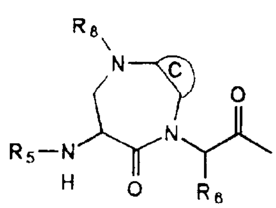
m is 1 or 2;

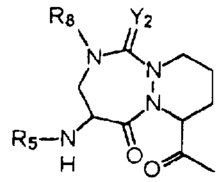
R_1 is selected from the group consisting of the following formulae:

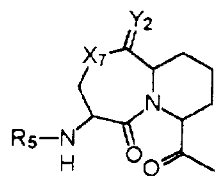
(e10)  ;

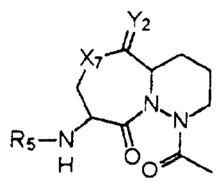
(e11)  ;

(e12)  ;

(w2)  ;

(y1)  ;

(y2)  ;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

-C(O)-CH_2-T_1-R_{11},

-C(O)-CH_2-F,

-C=N-O-R_9, and

-CO-Ar_2;

each R_5 is independently selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9,

-C(O)-N(R_{10})(R_{10})

-S(O)$_2$-R_9,

-S(O)$_2$-NH-R_{10},

$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

X_5 is $-\overset{|}{C}H-$ or $-\overset{|}{N}-$;

Y_2 is H_2 or O;

X_7 is $-N(R_8)-$ or $-O-$;

each T_1 is independently selected from the group consisting of $-O-$, $-S-$, $-S(O)-$, and $-S(O)_2-$;

R_6 is selected from the group consisting of $-H$ and $-CH_3$;

R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
$-H$, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein

the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

$-Ar_4$,

$-(CH_2)_{1-3}-Ar_4$,

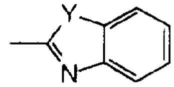
-H, and

$-C(O)-Ar_4$;

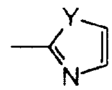
R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and a $-OC_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$:

(hh) 

, and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group consisting of -NH_2, -CO_2H, -Cl, -F, -Br, -I, -NO_2, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, -OR_5, -NHR_5, OR_9, -N(R_9)(R_{10}), R_9, -C(O)-R_{10}, and

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    CH2;
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  O
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provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferred compounds of embodiment E employ formula (II), wherein R_1 is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment E employ formula (II), wherein R_1 is (e12) and the other substituents are as defined above.

Other preferred compounds of embodiment E employ formula (II) wherein R_1 is (y1) and the other substituents are as defined above.

Other preferred compounds of embodiment E employ formula (II) wherein R_1 is (y2) and the other substituents are as defined above.

Other preferred compounds of embodiment E of employ formula (II) wherein R_1 is (z) and the other substituents are as defined above.

Other preferred compound of embodiment E employ formula (II) wherein R_1 is (w2) and the other substituents are as defined above.

More preferably, R_1 is (w2) and

m is 1;

ring C is benzo, pyrido, or thieno;

R_3 is selected from the group consisting of -C(O)-H, -C(O)-Ar_2, and -C(O)CH_2-T_1-R_{11};

R_5 is selected from the group consisting of:

-C(O)-R_{10}, wherein R_{10} is -Ar_3;

-C(O)O-R_9, wherein R_9 is -CH_2-Ar_3;

-C(O)C(O)-R_{10}, wherein R_{10} is -Ar_3;

-R_9, wherein R_9 is a C_{1-2} alkyl group substituted with -Ar_3; and

-C(O)C(O)-OR_{10}, wherein R_{10} is -CH_2Ar_3;

T_1 is O or S;

R_6 is H;

R_8 is selected from the group consisting -C(O)-R_{10}, -C(O)-CH_2-OR_{10}, and -C(O)CH_2-N(R_{10})(R_{10}), wherein R_{10} is H, CH_3, or -CH_2CH_3;

R_{11} is selected from the group consisting of -Ar_4, -$(CH_2)_{1-3}$-Ar_4, and -C(O)-Ar_4;

R_{15} is -OH or -OC_{1-4} straight or branched alkyl group optionally substituted with -Ar_3, -OH, -OR_9, or -CO_2H, wherein the R_9 is a -C_{1-4} branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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 O
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   CH2,
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 O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other preferred compounds of embodiment E employ formula (II) wherein R_1 is (e10), X_5 is CH, and the other substituents are as defined above.

More preferred compounds of embodiment E employ formula (II) wherein R_1 is (e10), X_5 is CH, R_3 is $CO\text{-}Ar_2$, and the other substituents are as defined above.

Other more preferred compounds of embodiment E employ formula (II) wherein R_1 is (e10), X_5 is CH, R_3 is $-C(O)-CH_2-T_1-R_{11}$, R_{11} is $-(CH_2)_{1-3}-Ar_4$, and the other substituents are as defined above.

Other more preferred compounds of embodiment E employ formula (II) wherein R_1 is (e10) and X_5 is CH and R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, R_{11} is $-C(O)-Ar_4$, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds,

m is 1;

T_1 is O or S;

R_{15} is -OH or $-OC_{1-4}$ straight or branched alkyl

group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

Ar_2 is (hh);

Y is O, and

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl, said cyclic group being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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     CH2,
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   O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$

straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other more preferred compounds of embodiment E employ formula (II) wherein R_1 is (e10), X_5 is CH, R_3 is -C(O)-H, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$, and
$-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-C(O)-R_{10}$,
$-R_9$, and
$-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds,

m is 1;

R_{15} is -OH or $-OC_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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        CH2,
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      O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$,

Other more preferred compounds of embodiment E employ formula (II) wherein R_1 is (e10) and X_5 is CH, R_3 is $-CO-CH_2-T_1-R_{11}$, and R_{11} is $-Ar_4$, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$, and
$-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-C(O)-R_{10}$,
$-R_9$, and
$-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds,

m is 1;

T_1 is O or S;

R_{15} is -OH or a $-OC_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

each Ar_3 cyclic group is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected

from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl, said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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    CH2,
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  O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other preferred compounds of embodiment E employ formula (II) wherein R_1 is (e10), X_5 is N, and the other substituents are as defined above.

More preferred compounds of embodiment E, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $CO-Ar_2$, and the other substituents are as defined above.

Other more preferred compounds of embodiment E, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $-C(O)-CH_2-T_1-R_{11}$, R_{11} is $-(CH_2)_{1-3}-Ar_4$, and the other substituents are as defined above.

Other more preferred compounds of embodiment E, employ formula (II) wherein R_1 is (e10) and X_5 is N and:

R_3 is $-C(O)-CH_2-T_1-R_{11}$;

T_1 is O; and

R_{11} is $-C(O)-Ar_4$, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds,

m is 1;

T_1 is O or S;

R_{15} is -OH or a $-OC_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

Ar_2 is (hh);

Y is O, and

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl, optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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    CH2,
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  O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other more preferred compounds of embodiment E, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is -C(O)-H, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

-C(O)-R_{10},
-C(O)O-R_9, and
-C(O)-NH-R_{10}.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

-S(O)$_2$-R_9,
-S(O)$_2$-NH-R_{10},
-C(O)-C(O)-R_{10},
-R_9, and
-C(O)-C(O)-OR_{10}.

Most preferably, in these more preferred compounds,

m is 1;

R_{15} is -OH or -OC_{1-4} straight or branched alkyl group optionally substituted with -Ar_3, -OH, -OR_9, or -CO_2H, wherein the R_9 is a -C_{1-4} branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or -CH_3;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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 O
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   CH2,
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 O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other more preferred compounds of embodiment E, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $-CO-CH_2-T_1-R_{11}$, R_{11} is $-Ar_4$, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-C(O)-R_{10}$,
$-R_9$, and
$-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds

m is 1;

T_1 is O or S;

R_{15} is -OH or $-OC_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl,

said cyclic group being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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  O
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    CH2,
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  O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

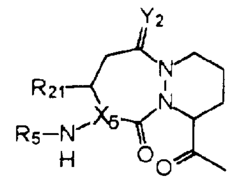
provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

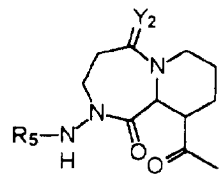
The ICE inhibitors of another embodiment (F) of this invention are those of formula (<u>III</u>):

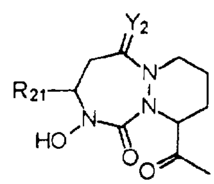
$$\text{(III)} \qquad \begin{array}{c} R_1\text{-}N\text{-}R_2 \\ | \\ H \end{array}$$

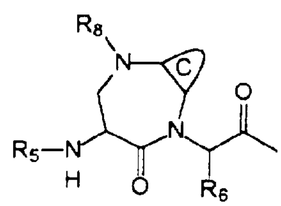
wherein:

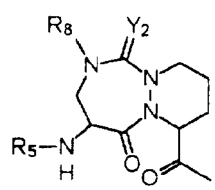
R_1 is selected from the group consisting of the following formulae:

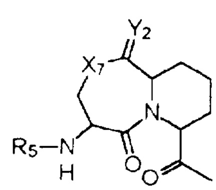
(e10)  ;

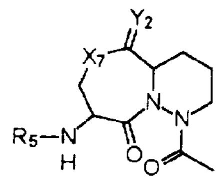
(e11)  ;

(e12)  ;

(w2)  ;

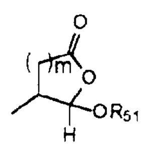
(y1)  ;

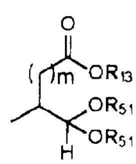
(y2)  ;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_2 is:

(a)  , or

(b)  ;

m is 1 or 2;

each R_5 is independently selected from the group consisting of:

-C(O)-R_{10},
-C(O)O-R_9,
-C(O)-N(R_{10})(R_{10})
-S(O)$_2$-R_9,
-S(O)$_2$-NH-R_{10},
-C(O)-CH_2-O-R_9,
-C(O)C(O)-R_{10},
-R_9,
-H,

$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

X_5 is CH or N;

Y_2 is H_2 or O;

X_7 is $-N(R_8)-$ or $-O-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(H)-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$;
$-C(O)-CH_2N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is

optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each R_{51} is independently selected from the group consisting of R_9, $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, OR_9, $-N(R_9)(R_{10})$, R_9, $-C(O)-R_{10}$, and

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provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferred compounds of embodiment F employ formula (III), wherein R_1 is (w2) and the other substituents are as defined above.

Preferably, when R_1 is (w2):

m is 1;

ring C is benzo, pyrido, or thieno;

R_5 is selected from the group consisting of:
$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$;
$-C(O)O-R_9$, wherein R_9 is $-CH_2-Ar_3$;
$-C(O)C(O)-R_{10}$, wherein R_{10} is $-Ar_3$;
$-R_9$, wherein R_9 is a C_{1-2} alkyl group substituted with $-Ar_3$; and
$-C(O)C(O)-OR_{10}$, wherein R_{10} is $-CH_2Ar_3$;

R_6 is H;

R_8 is selected from the group consisting $-C(O)-R_{10}$, $-C(O)-CH_2-OR_{10}$, and $-C(O)CH_2-N(R_{10})(R_{10})$, wherein R_{10} is H, CH_3, or $-CH_2CH_3$;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with Ar_3, $-OH$, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (e12) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (y1) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (y2) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (z) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (e10) and X_5 is CH (also referred to herein as e10-B), and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (e10) and X_5 is N, (also referred to herein as e10-A) and the other substituents are as defined above.

Preferably, when R_1 is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B), R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

Alternatively, when R_1 is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B), R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$,

$-C(O)-C(O)-OR_{10}$, and

$-C(O)C(O)-N(R_9)(R_{10})$.

More preferably, R_5 is $R-C(O)-C(O)-R_{10}$.

Alternatively, R_5 is -C(O)-C(O)-OR_{10}.

More preferably when R_1 is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B):

m is 1;

R_{21} is -H or -CH_3;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein the Ar_3 cyclic group is phenyl, said cyclic group optionally being multiply or singly substituted by -Q_1;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group consisting of -NH_2, -Cl, -F, -Br, -OH, -R_9, -NH-R_5 wherein R_5 is -C(O)-R_{10} or -S(O)$_2$-R_9, -OR_5 wherein R_5 is -C(O)-R_{10}, -OR_9, -N(R_9)(R_{10}), and

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   CH2,
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wherein each R_9 and R_{10} are independently a -C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein the Ar_3 cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by -Q_1;

provided that when $-Ar_3$ is substituted with a $-Q_1$ group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

More preferably, in these more preferred compounds, the Ar_3 cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Compounds in a preferred form of this embodiment F are those wherein:

R_5 is $-C(O)-R_{10}$, wherein:

R_{10} is Ar_3, wherein the Ar_3 cyclic group is phenyl, said cyclic group optionally being singly or multiply substituted by:

-F,

-Cl,

$-N(H)-R_5$, wherein $-R_5$ is -H or $-C(O)-R_{10}$, wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the Ar_3 cyclic group is phenyl, said cyclic group optionally being singly or multiply substituted by $-Q_1$,

$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a $-C_{1-4}$ straight or branched alkyl group, or

$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or branched alkyl group.

More preferably the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by $-NH-R_5$, $-N(R_9)(R_{10})$, or $-O-R_5$.

Other preferred compounds of embodiment F include those wherein R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of indolyl, benzimidazolyl, thienyl, and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

Other preferred compounds of embodiment F include those wherein R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Other preferred compounds of embodiment F are those wherein R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3, wherein the Ar_3 cyclic group is phenyl, substituted by

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   CH2
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 O   .
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In another form of embodiment F the compounds are as described above, further provided that when:

m is 1;
R_1 is (e10);
X_5 is CH;
R_{15} is -OH;
R_{21} is -H; and

Y_2 is O and R_3 is -C(O)-H, then R_5 cannot be:

-C(O)-R_{10}, wherein R_{10} is -Ar_3 and the Ar_3 cyclic group is phenyl, unsubstituted by -Q_1, 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

-C(O)-OR_9, wherein R_9 is -CH_2-Ar_3, and the Ar_3 cyclic group is phenyl, unsubstituted by -Q_1,; and when

Y_2 is O, R_3 is -C(O)-CH_2-T_1-R_{11}, T_1 is O, and R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

-C(O)-R_{10}, wherein R_{10} is -Ar_3 and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl, 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

-C(O)-OR_9, wherein R_9 is -CH_2-Ar_3 and the Ar_3 cyclic group is phenyl;

and when R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

-C(O)-OR_9, wherein R_9 is -CH_2-Ar_3, and the Ar_3 cyclic group is phenyl;

and when R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

-C(O)-R_{10}, wherein R_{10} is -Ar_3 and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, or

-C(O)-OR_9, wherein R_9 is -CH_2-Ar_3, and the Ar_3 cyclic group is phenyl, unsubstituted by -Q_1,; and when

Y_2 is O, R_3 is -C(O)-CH_2-T_1-R_{11}, T_1 is O, and R_{11} is -C(O)-Ar_4, wherein the Ar_4 cyclic group is 2,5-

dichlorophenyl, then R_5 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methyl)phenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benztriazolyl, N-carboethoxy-5-benztriazolyl, N-carboethoxy-5-benzimidazolyl, or

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$,; and when

Y_2 is H_2, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is
$-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl.

In another form of embodiment F, preferred compounds are those wherein R_{21} is -H.

Alternatively, preferred compounds are those wherein R_{21} is $-CH_3$.

Preferred compounds of embodiment F employ formula (III), wherein R_1 is (w2) and the other substituents are as defined above.

More preferably, R_1 is (w2) and

m is 1;

ring C is benzo, pyrido, or thieno;

R_3 is selected from the group consisting of $-C(O)-H$, $-C(O)-Ar_2$, and $-C(O)CH_2-T_1-R_{11}$;

R_5 is selected from the group consisting of:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$;

$-C(O)O-R_9$, wherein R_9 is $-CH_2-Ar_3$;

$-C(O)C(O)-R_{10}$, wherein R_{10} is $-Ar_3$;

$-R_9$, wherein R_9 is a C_{1-2} alkyl group substituted with $-Ar_3$; and

$-C(O)C(O)-OR_{10}$, wherein R_{10} is $-CH_2Ar_3$;

T_1 is O or S;

R_6 is H;

R_8 is selected from the group consisting $-C(O)-R_{10}$, $-C(O)-CH_2-OR_{10}$, and $-C(O)CH_2-N(R_{10})(R_{10})$, wherein R_{10} is H, CH_3, or $-CH_2CH_3$;

R_{11} is selected from the group consisting of $-Ar_4$, $-(CH_2)_{1-3}-Ar_4$, and $-C(O)-Ar_4$;

R_{15} is -OH or $-OC_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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  O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (e12) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III) wherein R_1 is (y1) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III) wherein R_1 is (y2) and the other substituents are as defined above.

Other preferred compounds of embodiment F of employ formula (III) wherein R_1 is (z) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III) wherein R_1 is (e10), X_5 is CH, and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III) wherein R_1 is (e10), X_5 is N, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$, and
$-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-C(O)-R_{10}$,
$-R_9$,
$-C(O)-C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$.

Most preferably, in these more preferred compounds,

m is 1;

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl

group optionally substituted with $-Ar_3$, -OH, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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 O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted

with another $-Ar_3$.

Preferred compounds of embodiment (F) include, but are not limited to:

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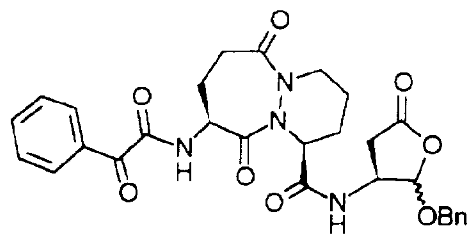

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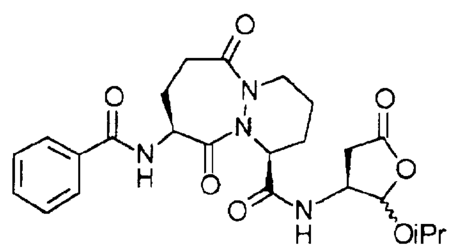

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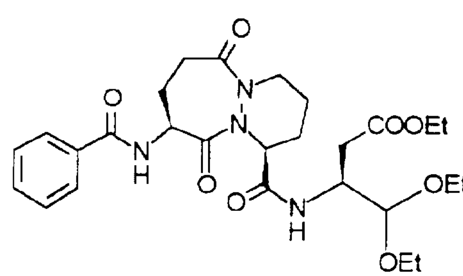

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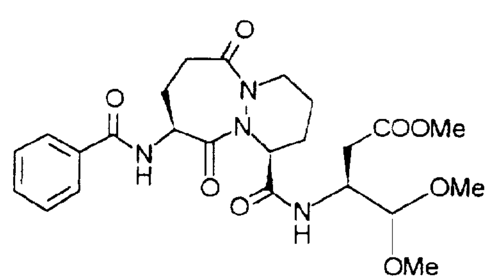

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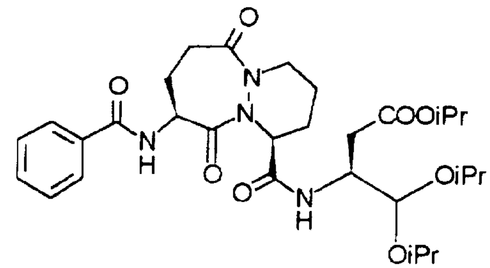

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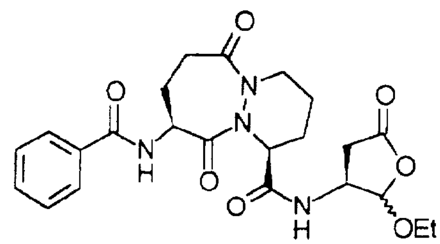
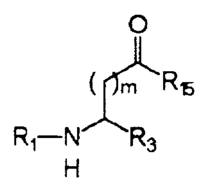


The ICE inhibitors of another embodiment (G) of this invention are those of formula (IV):

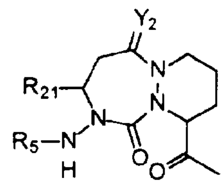
(IV)

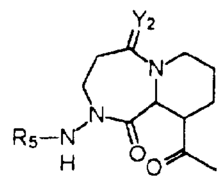


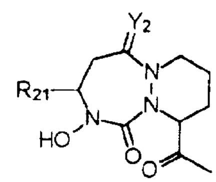
wherein:

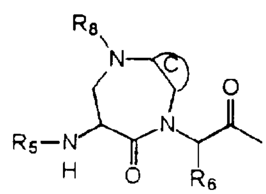
m is 1 or 2;

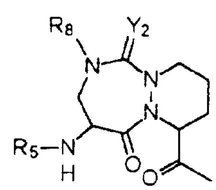
R_1 is selected from the group consisting of the following formulae:

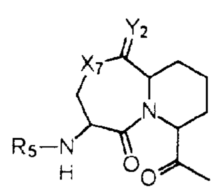
(e10-A)  ;

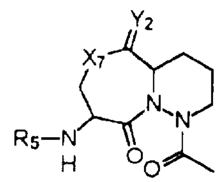
(e11)  ;

(e12)  ;

(w2)  ;

(y1)  ;

(y2)  ;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

-C(O)-CH_2-T_1-R_{11},

-C(O)-CH_2-F,

-C=N-O-R_9, and

-CO-Ar_2;

each R_5 is independently selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9,

-C(O)-N(R_{10})(R_{10})

-S(O)$_2$-R_9,

-S(O)$_2$-NH-R_{10},

-C(O)-CH_2-O-R_9,

-C(O)C(O)-R_{10},

-R_9,

-H,

-C(O)C(O)-OR_{10}, and

-C(O)C(O)-N(R_9)(R_{10});

Y_2 is H_2 or O;

X_7 is -N(R_8)- or -O-;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

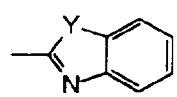
$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and

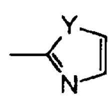
-C(O)-Ar_4;

R_{15} is selected from the group consisting of -OH, -OAr_3, -N(H)-OH, and -OC_{1-6}, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with Ar_3, -$CONH_2$, -OR_5, -OH, -OR_9, or -CO_2H;

each R_{21} is independently selected from the group consisting of -H or a -C_{1-6} straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q_1 or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or

multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, OR_9, $-N(R_9)(R_{10})$, R_9, $-C(O)-R_{10}$, and

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provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$;

Preferred compounds of embodiment G employ formula (IV), wherein R_1 is (w2) and the other substituents are as defined above.

Preferably, when R_1 is (w2):

m is 1;

ring C is benzo, pyrido, or thieno;

R_5 is selected from the group consisting of:

-C(O)-R_{10}, wherein R_{10} is -Ar_3;

-C(O)O-R_9, wherein R_9 is -CH_2-Ar_3;

-C(O)C(O)-R_{10}, wherein R_{10} is -Ar_3;

-R_9, wherein R_9 is a C_{1-2} alkyl group substituted with -Ar_3; and

-C(O)C(O)-OR_{10}, wherein R_{10} is -CH_2Ar_3;

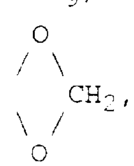
R_6 is H;

R_8 is selected from the group consisting -C(O)-R_{10}, -C(O)-CH_2-OR_{10}, and -C(O)CH_2-N(R_{10})(R_{10}), wherein R_{10} is H, CH_3, or -CH_2CH_3;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with Ar_3, -OH, -OR_9, -CO_2H, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl;

each Q_1 is independently selected from the group consisting of -NH_2, -Cl, -F, -Br, -OH, -R_9, -NH-R_5 wherein R_5 is -C(O)-R_{10} or -S(O)$_2$-R_9, -OR_5 wherein R_5 is -C(O)-R_{10}, -OR_9, -NHR_9, and



wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (e10-A) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (e12) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (y1) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (y2) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (z) and the other substituents are as defined above.

More preferred compounds of embodiment G are those wherein R_3 is $-CO-Ar_2$.

Most preferably, when R_3 is -CO-Ar_2, Y is O.

Other more preferred compounds are those wherein R_3 is -C(O)-CH_2-T_1-R_{11} and R_{11} is -$(CH_2)_{1-3}$-Ar_4.

Most preferably, when R_3 is -C(O)-CH_2-T_1-R_{11} and R_{11} is -$(CH_2)_{1-3}$-Ar_4, T_1 is O.

Other more preferred compounds are those wherein:

R_3 is -C(O)-CH_2-T_1-R_{11};
T_1 is O; and
R_{11} is -C(O)-Ar_4.

Other more preferred compounds are those wherein R_3 is -C(O)-H.

Other more preferred compounds are those wherein R_3 is -CO-CH_2-T_1-R_{11} and R_{11} is -Ar_4.

More preferably, when R_3 is -CO-CH_2-T_1-R_{11} and R_{11} is -Ar_4, T_1 is O or S.

More preferably, when R_1, is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B), R_5 is selected from the group consisting of:

-C(O)-R_{10},
-C(O)O-R_9, and
-C(O)-NH-R_{10}.

Alternatively, when R_1, is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B), R_5 is selected from the group consisting of:

-$S(O)_2$-R_9,
-$S(O)_2$-NH-R_{10},
-C(O)-C(O)-R_{10},
-R_9,

$-C(O)-C(O)-OR_{10}$, and
$-C(O)-C(O)-N(R_9)(R_{10})$.

More preferably, R_5 is $-C(O)-C(O)-R_{10}$.

Alternatively, R_5 is $-C(O)-C(O)-OR_{10}$.

Most preferably, when R_1 is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B),:

m is 1;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein the Ar_3 cyclic group is phenyl, said cyclic group optionally being multiply or singly substituted by $-Q_1$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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 O
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   CH2,
\ /
 O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the Ar_3 cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

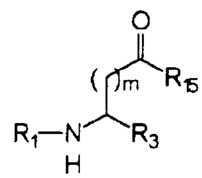
provided that when $-Ar_3$ is substituted with a $-Q_1$ group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

More preferably, in these more preferred compounds, the Ar_3 cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Compounds in a preferred form of embodiment G are those wherein R_{21} is H and the other substituents are as defined above.

Compounds in another preferred form of embodiment G are those wherein R_{21} is CH_3 and the other substituents are as defined above.

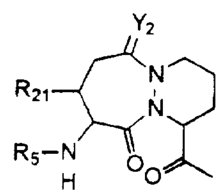
The ICE inhibitors of another embodiment (H) of this invention are those of formula (V):

(V) 

wherein:

m is 1 or 2;

R_1 is:

(e10-B)  ;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

$-C(O)-CH_2-T_1-R_{11}$,

$-C(O)-CH_2-F$,

$-C=N-O-R_9$, and

$-CO-Ar_2$;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$-C(O)-N(R_{10})(R_{10})$

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-CH_2-O-R_9$,

$-C(O)C(O)-R_{10}$,

$-R_9$,

-H, and

$-C(O)C(O)-N(R_9)(R_{10})$, and

$-C(O)C(O)-OR_{10}$;

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

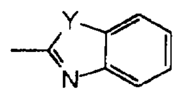
each R_{11} is independently selected from the group consisting of:

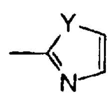
$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and
$-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with Ar_3,
$-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

R_{21} is $-CH_3$;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected

from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group consisting of -NH_2, -CO_2H, -Cl, -F, -Br, -I, -NO_2, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, -OR_5, -NHR_5, OR_9, -N(R_9)(R_{10}), R_9, -C(O)-R_{10}, and

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 O
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   CH2;
\ /
 O
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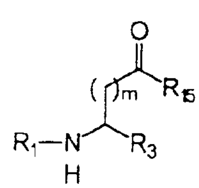
provided that when -Ar_3 is substituted with a Q_1 group which comprises one or more additional -Ar_3 groups, said additional -Ar_3 groups are not substituted with another -Ar_3;

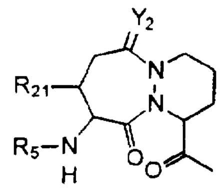
Compounds of another form of embodiment (I) (form 1) are those of formula (V):

(V) 

wherein:

m is 1 or 2;

R_1 is:

(e10-B)  ;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

-C(O)-CH_2-T_1-R_{11},

-C(O)-CH_2-F,

-C=N-O-R_9, and

-CO-Ar_2;

each R_5 is -C(O)C(O)-OR_{10};

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)$_2$-;

R_8 is selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9,

-C(O)-NH-R_{10},

-S(O)$_2$-R_9,

-S(O)$_2$-NH-R_{10},

-C(O)-CH_2-OR_{10},

-C(O)C(O)-R_{10},

-C(O)-CH_2-N(R_{10})(R_{10}),

-C(O)-CH_2C(O)-O-R_9,

-C(O)-CH_2C(O)-R_9,

-H, and

-C(O)-C(O)-OR_{10};

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

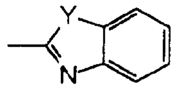
each R_{11} is independently selected from the group consisting of:

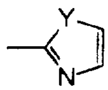
$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and
$-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with Ar_3, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group

consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, OR_9, $-N(R_9)(R_{10})$, R_9, $-C(O)-R_{10}$, and

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 O
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   CH2;
\ /
 O
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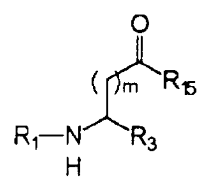
provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$;

Alternatively, compounds of this form of embodiment I (form 2) are those wherein R_{21} is $-CH_3$.

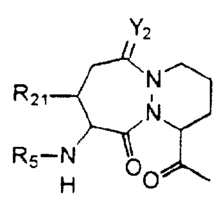
Compounds of another form of embodiment (J) (form 1) are those of formula (V):

(V) 

wherein:

m is 1 or 2;

R_1 is:

(e10-B) 

;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

$-C(O)-CH_2-T_1-R_{11}$,
$-C(O)-CH_2-F$,
$-C=N-O-R_9$, and
$-CO-Ar_2$;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(R_{10})(R_{10})$
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
$-H$,

$-C(O)-C(O)-OR_{10}$, and
$-C(O)-C(O)-N(R_9)(R_{10})$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

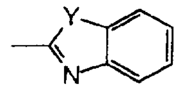
each R_{11} is independently selected from the group consisting of:

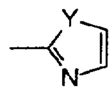
$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and
$-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with Ar_3,
$-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group

consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, OR_9, $-N(R_9)(R_{10})$, R_9, $-C(O)-R_{10}$, and

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  O
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    CH2;
 \ /
  O
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provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$;

provided that when:

m is 1;
R_1 is (e10);
X_5 is CH;
R_{15} is -OH;
R_{21} is -H; and

Y_2 is O and R_3 is -C(O)-H, then R_5 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$, 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$,; and when

Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl,4-(carboxyethylthio)phenyl, 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-

fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

-C(O)-OR$_9$, wherein R$_9$ is -CH$_2$-Ar$_3$ and the Ar$_3$ cyclic group is phenyl;

and when R$_{11}$ is Ar$_4$, wherein the Ar$_4$ cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl), then R$_5$ cannot be:

-C(O)-OR$_9$, wherein R$_9$ is -CH$_2$-Ar$_3$, and the Ar$_3$ cyclic group is phenyl;

and when R$_{11}$ is Ar$_4$, wherein the Ar$_4$ cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then R$_5$ cannot be:

-C(O)-R$_{10}$, wherein R$_{10}$ is -Ar$_3$ and the Ar$_3$ cyclic group is 4-(dimethylaminomethyl)phenyl, or

-C(O)-OR$_9$, wherein R$_9$ is -CH$_2$-Ar$_3$, and the Ar$_3$ cyclic group is phenyl, unsubstituted by -Q$_1$,; and when

Y$_2$ is O, R$_3$ is -C(O)-CH$_2$-T$_1$-R$_{11}$, T$_1$ is O, and R$_{11}$ is -C(O)-Ar$_4$, wherein the Ar$_4$ cyclic group is 2,5-dichlorophenyl, then R$_5$ cannot be:

-C(O)-R$_{10}$, wherein R$_{10}$ is -Ar$_3$ and the Ar$_3$ cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methyl)phenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benztriazolyl, N-carboethoxy-5-benztriazolyl, N-carboethoxy-5-benzimidazolyl, or

-C(O)-OR$_9$, wherein R$_9$ is -CH$_2$-Ar$_3$, and the Ar$_3$ cyclic group is phenyl, unsubstituted by -Q$_1$,; and when

Y$_2$ is H$_2$, R$_3$ is -C(O)-CH$_2$-T$_1$-R$_{11}$, T$_1$ is O, and R$_{11}$ is
-C(O)-Ar$_4$, wherein the Ar$_4$ cyclic group is 2,5-dichlorophenyl, then R$_5$ cannot be:

-C(O)-OR$_9$, wherein R$_9$ is -CH$_2$-Ar$_3$ and the Ar$_3$

cyclic group is phenyl.

Compounds of another form of embodiment J (form 2) are those wherein R_{21} is $-CH_3$.

Compounds of another form of embodiment J (form 3) are those wherein R_5 is $-C(O)-C(O)-OR_{10}$.

Compounds of another form of embodiment J (form 4) are those wherein R_5 is $-C(O)-C(O)-OR_{10}$ and R_{21} is $-CH_3$.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-CO-Ar_2$.

More preferably, when R_3 is $-CO-Ar_2$ Y is O.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-C(O)-CH_2-T_1-R_{11}$ and R_{11} is $-(CH_2)_{1-3}-Ar_4$.

More preferably, when R_3 is $-C(O)-CH_2-T_1-R_{11}$ and R_{11} is $-(CH_2)_{1-3}-Ar_4$, T_1 is O.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is $-C(O)-Ar_4$.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-C(O)-H$.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-CO-CH_2-T_1-R_{11}$ and R_{11} is $-Ar_4$.

More preferably, when R_3 is $-CO-CH_2-T_1-R_{11}$ and

R_{11} is $-Ar_4$, T_1 is O or S.

More preferred compounds of embodiments H and J (forms 1 and 2) are those wherein R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

Alternatively, more preferred compounds of embodiments H and J (forms 1 and 2) are those wherein R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$,

$-C(O)-C(O)-OR_{10}$, and

$-C(O)-C(O)-N(R_9)(R_{10})$.

Most preferably, R_5 is $-C(O)-C(O)-R_{10}$.

Alternatively, R_5 is $-C(O)-C(O)-OR_{10}$.

More preferred compounds of embodiments H, I (form 2), and J (forms 2 and 4) are those wherein:

m is 1;

Y_2 is O;

R_{15} is -OH or $-OC_{1-4}$ straight or branched alkyl group optionally substituted with Ar_3, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

Ar_2 is (hh);

Y is O, and

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the group consisting of phenyl, tetrazolyl, pyridyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein the Ar_3 cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted

with another $-Ar_3$.

More preferred compounds of embodiments I (form 1), and J (form 3) are those wherein:

m is 1;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein the Ar_3 cyclic group is phenyl, said cyclic group optionally being multiply or singly substituted by $-Q_1$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and

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   CH2,
\ /
 O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the Ar_3 cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

provided that when $-Ar_3$ is substituted with a $-Q_1$ group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferably, in these more preferred compounds the Ar_3 cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Preferred compounds of embodiments H, and J (forms 1 and 1) are those wherein:

R_3 is $-C(O)-CH_2-T_1-R_{11}$;

T_1 is O; and

R_{11} is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is selected from the set consisting of tetrazolyl, pyridyl, oxazolyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-CO-CH_2-T_1-R_{11}$, R_{11} is $-Ar_4$, wherein the Ar_4 cyclic group is pyridyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Preferred compounds of embodiment J (form 1) are those wherein:

R_3 is $-C(O)-H$, and

R_5 is -C(O)-R_{10}, wherein:

R_{10} is Ar_3, wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

-F,

-Cl,

-N(H)-R_5, wherein -R_5 is -H or -C(O)-R_{10}, wherein R_{10} is a -C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl,

-N(R_9)(R_{10}), wherein R_9 and R_{10} are independently a -C_{1-4} straight or branched alkyl group, or

-O-R_5, wherein R_5 is H or a -C_{1-4} straight or branched alkyl group.

More preferably, Ar_3 is phenyl being optionally singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R_5, -N(R_9)(R_{10}), or -O-R_5.

Other more preferred compounds of embodiment J (form 1) are those wherein:

R_3 is -C(O)-H;

R_5 is -C(O)-R_{10}, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q_1;

Other more preferred compounds of embodiment J (form 1) are those wherein:

R_3 is -C(O)-H;

R_5 is -C(O)-R_{10}, wherein R_{10} is Ar_3 and the Ar_3

cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Other more preferred compounds of embodiment J (form 1) are those wherein:

R_3 is -C(O)-H;

R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is phenyl, substituted by

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Preferred compounds of embodiment (J) include, but are not limited to:

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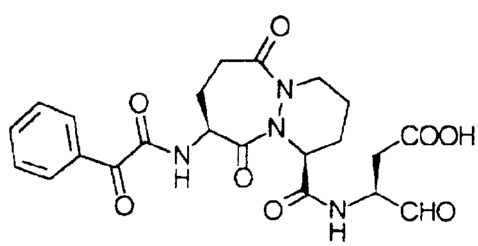
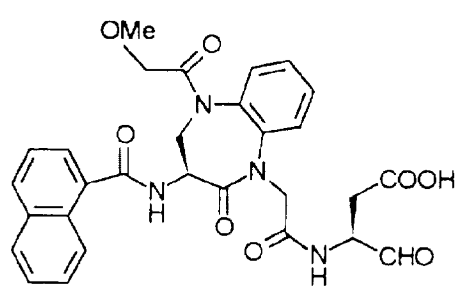


2201



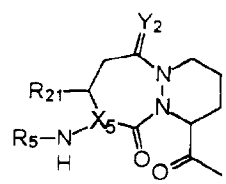
The ICE inhibitors of another embodiment (K) of this invention are those of formula:

$$\text{(VI)} \qquad \begin{array}{c} R_1\text{-N-}R_2 \\ | \\ \text{H} \end{array}$$

wherein:

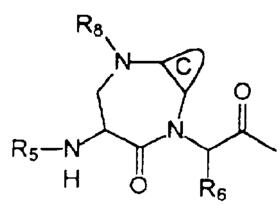
R_1 is:

(e10)



, or

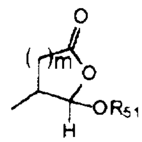
(w2)

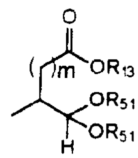


;

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl; the ring optionally being singly or multiply substituted by $-Q_1$;

R_2 is:

(a)  , or

(b)  ;

m is 1 or 2;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(R_{10})(R_{10})$
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

X_5 is CH or N;

Y_2 is H_2 or O;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(H)-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$;
$-C(O)-CH_2N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9, $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

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provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferred compounds of this embodiment are those wherein:

m is 1;

C is a ring chosen from the set consisting of benzo, pyrido, or thieno the ring optionally being singly or multiply substituted by halogen, $-NH_2$, $-NH-R_5$, $-NH-R_9$, $-OR_{10}$, or $-R_9$, wherein R_9 is a straight or branched C_{1-4} alkyl group and R_{10} is H or a straight or branched C_{1-4} alkyl group;

R_6 is H;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with Ar_3, $-OH$, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is $-H$ or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-CH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

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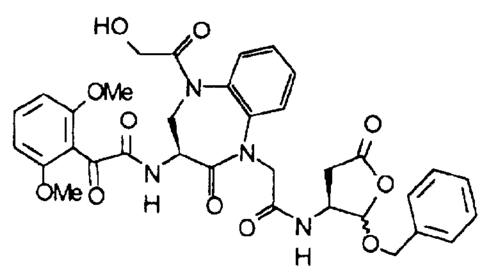
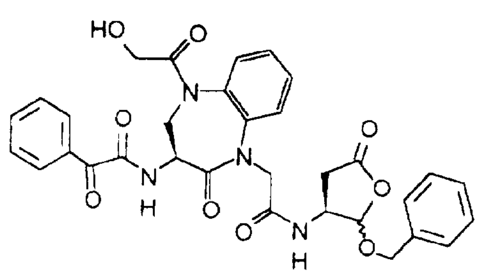
wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferably, in this preferred embodiment, R_1 is (w2) and the other substituents are as defined above.

Compounds of this preferred embodiment include, but are not limited to:

677  ; and

680  .

More preferably, R_8 is selected from the

group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$-C(O)-CH_2-OR_{10}$, and

$-C(O)-CH_2C(O)-R_9$.

Most preferably, R_8 is $-C(O)-CH_2-OR_{10}$ and R_{10} is $-H$ or $-CH_3$.

Alternatively, in this preferred embodiment, R_1 is (e10) and X_5 is CH and the other substituents are as defined above.

Alternatively, in this preferred embodiment, R_1 is (e10) and X_5 is N and the other substituents are as defined above.

Preferably, in any of the above compounds of embodiment (K), R_5 is $-C(O)-R_{10}$ or $-C(O)-C(O)-R_{10}$ and the other substituents are as defined above.

More preferably, R_{10} is $-Ar_3$ and the other substituents are as defined above.

More preferably, in these more preferred compounds:

R_5 is $-C(O)-R_{10}$ and R_{10} is Ar_3,

wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

$-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group;

$-F$,

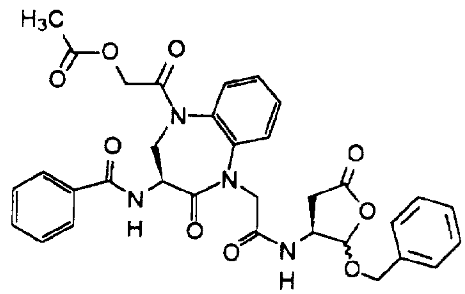
$-Cl$,

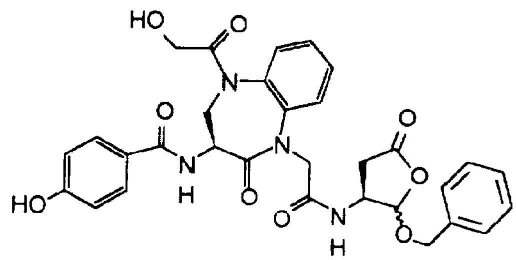
$-N(H)-R_5$, wherein $-R_5$ is $-H$ or $-C(O)-R_{10}$, wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl,

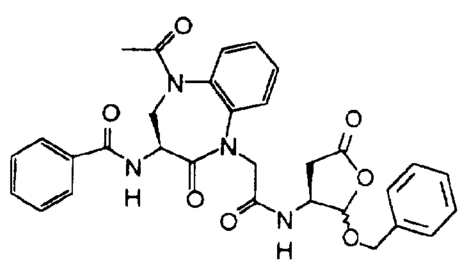
$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a $-C_{1-4}$ straight or branched alkyl group, or

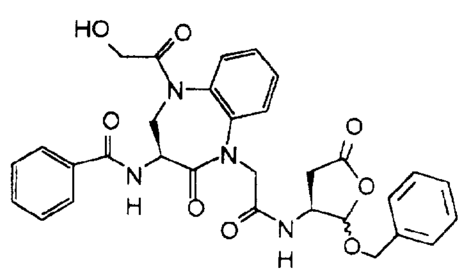
$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or branched alkyl group.

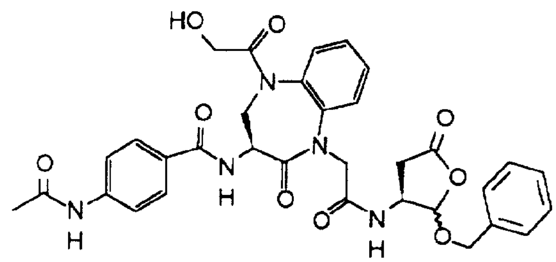
Preferred compounds of this more preferred embodiment include, but are not limited to:

682  ;

690b  ;

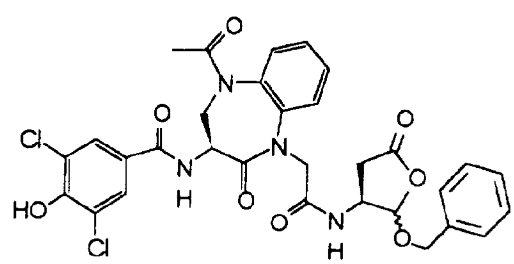
693  ;

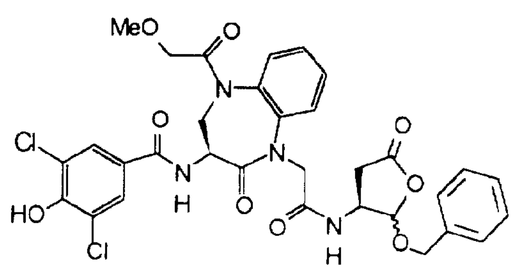
695a  ;

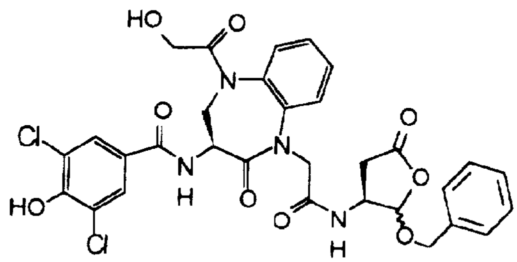
695b  .

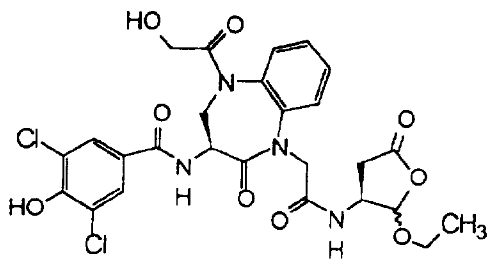
Most preferably, Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by $-NH-R_5$, $-N(R_9)(R_{10})$, or $-O-R_5$.

Preferred compounds of this most preferred embodiment include, but are not limited to:

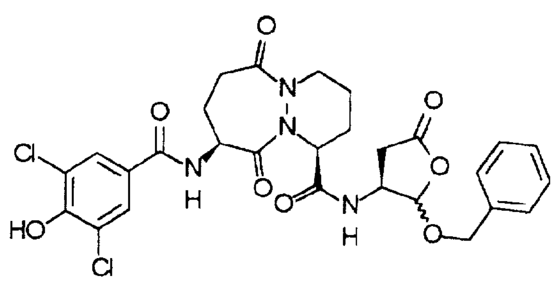
655  ;

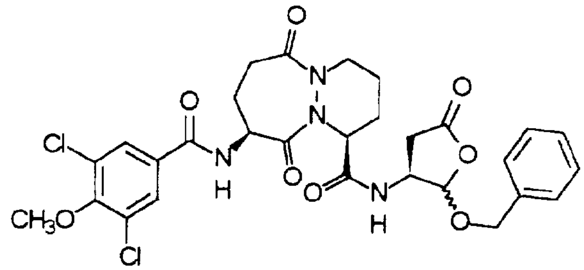
688a  ;

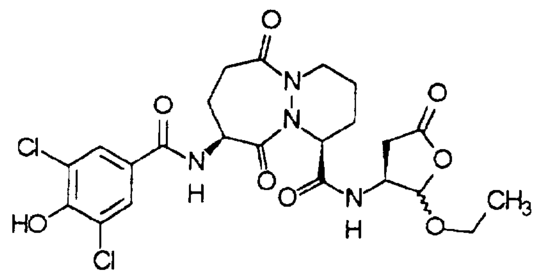
692a  ;

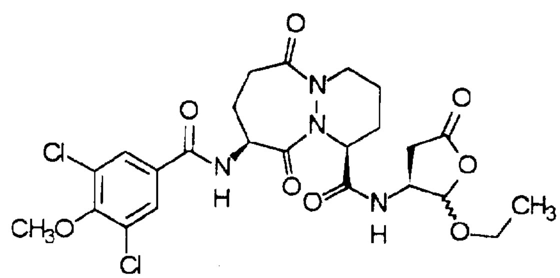
692b  .

Other preferred compounds of this most preferred embodiment include, but are not limited to:

213k  ;

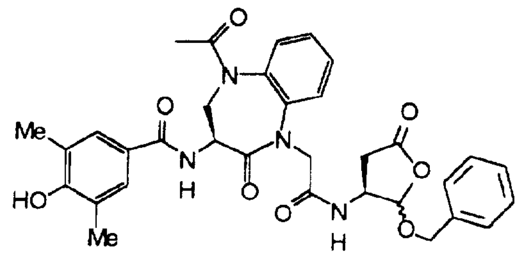
213m  ;

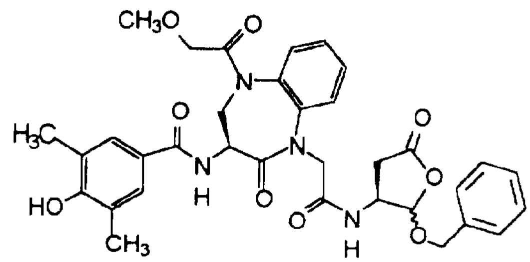
550k  ; and

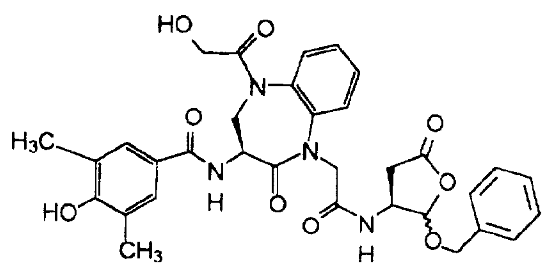
550m  .

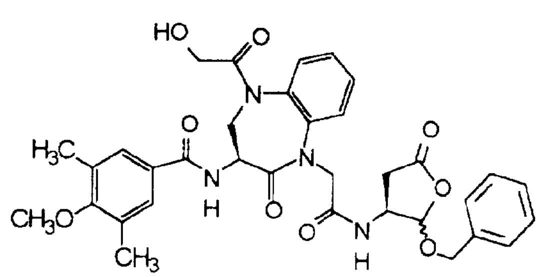
Alternatively, Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by $-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group; and at the 4-position by $-O-R_5$.

Preferred compounds of this most preferred embodiment include, but are not limited to:

670  ;

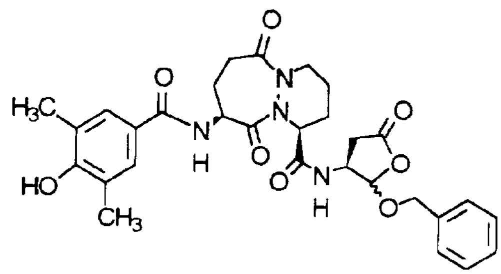
688b  ;

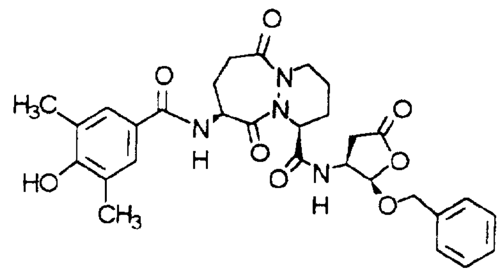
690a  ;

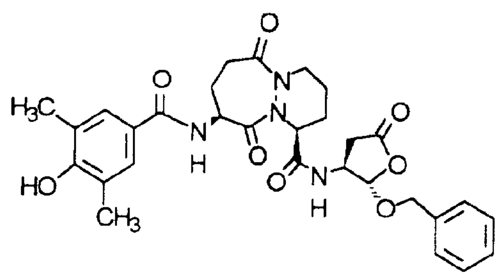
695c  .

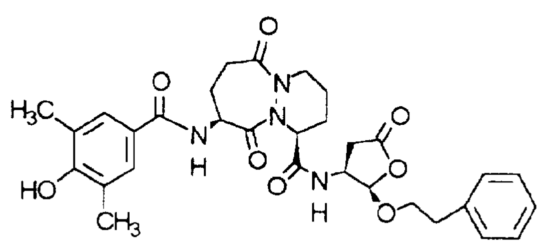
Other preferred compounds of this most preferred embodiment include, but are nct

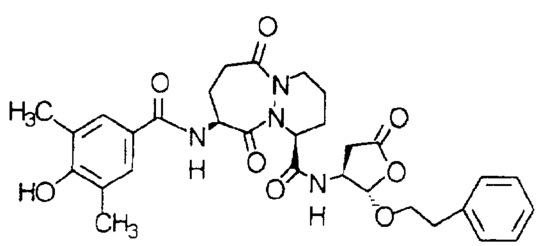
limited to:

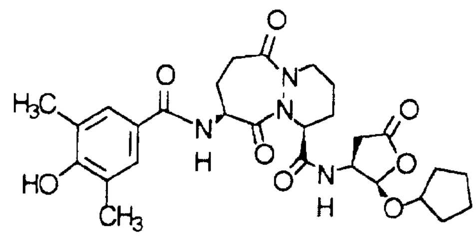
214w-1  ;

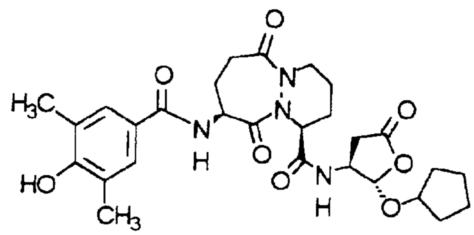
214w-2  ;

214w-3  ;

214w-4  ;

214w-5  ;

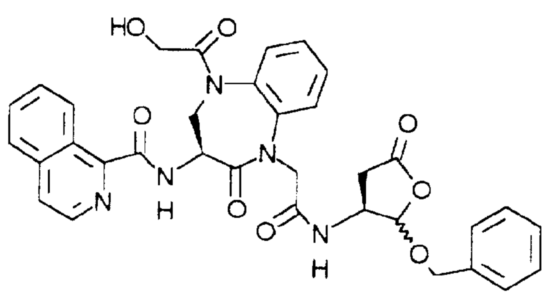
214w-6  ; and

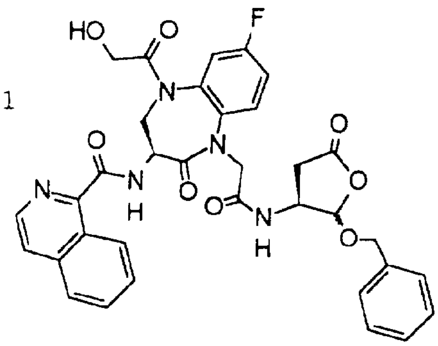
214w-7  .

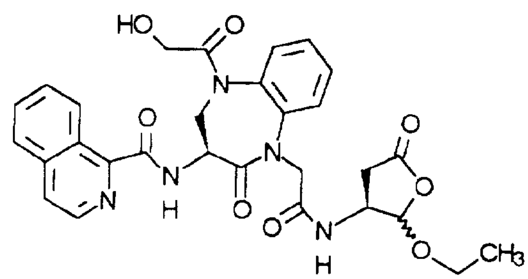
Alternatively, in this more preferred embodiment, R_5 is -C(O)-R_{10}, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q_1.

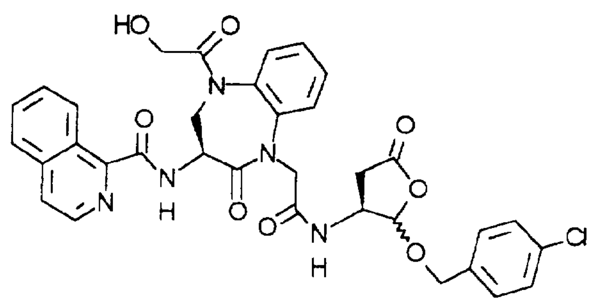
Most preferably, the Ar_3 cyclic group is isoquinolyl.

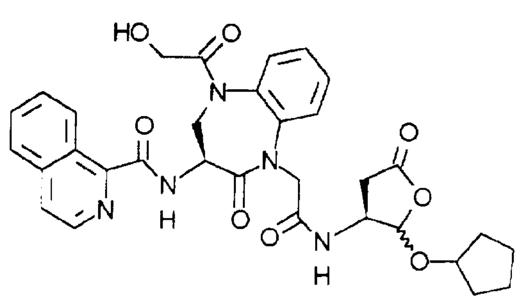
Preferred compounds of this most preferred embodiment include, but are not limited to:

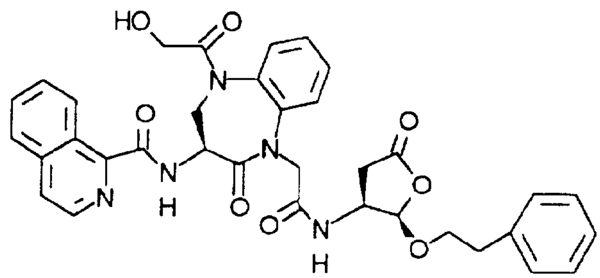
696a  ;

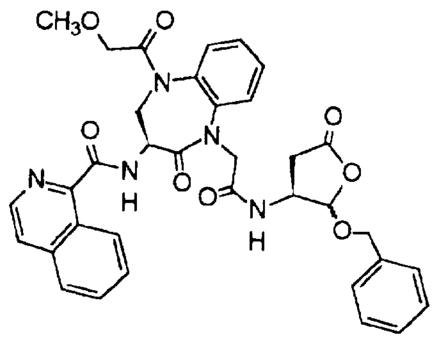
696a-1  ;

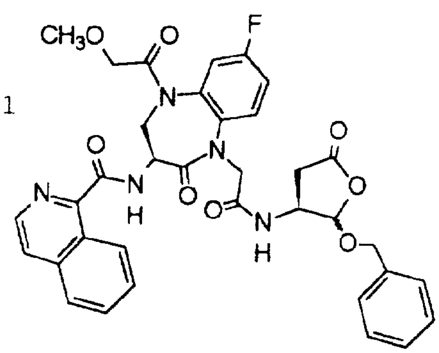
696b  ;

696c  ;

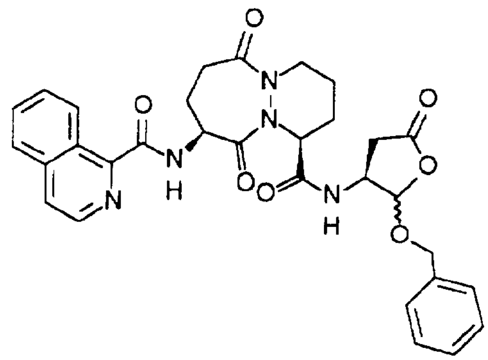
696d  ;

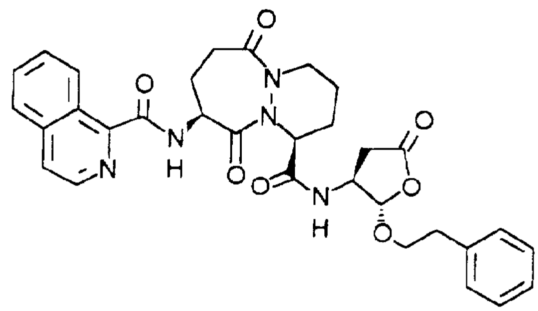
696e  ; and

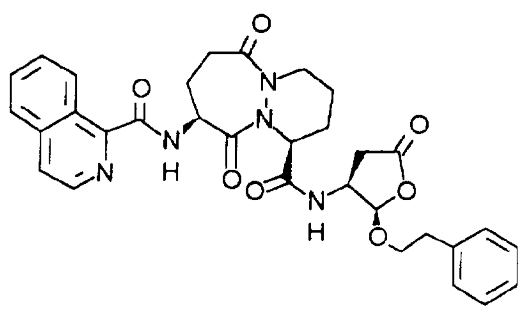
699a  ; and

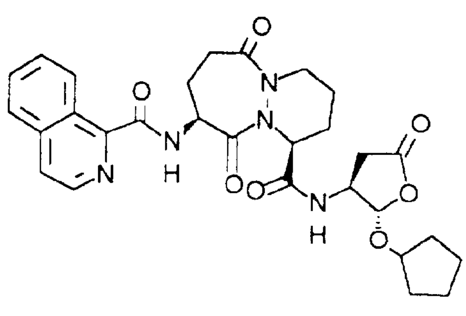
699a-1  .

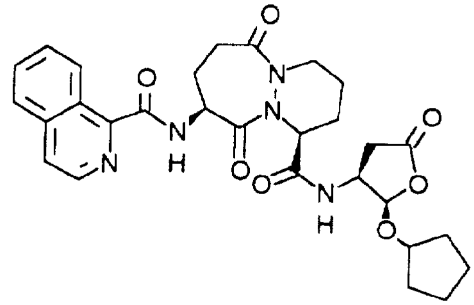
Other preferred compounds of this most preferred embodiment include, but are not limited to:

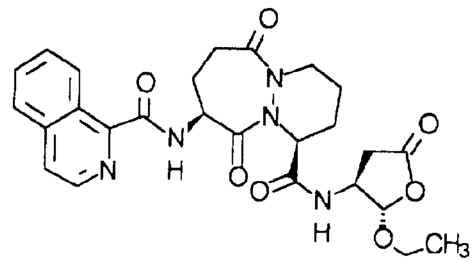
213y  ;

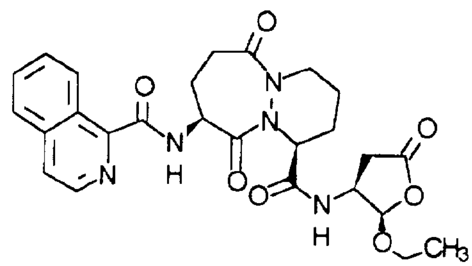
412a  ;

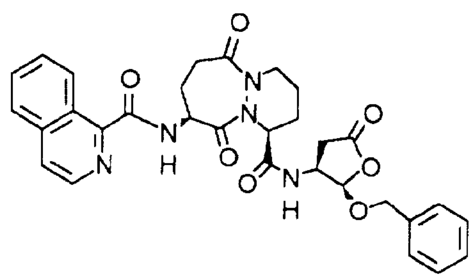
412b  ;

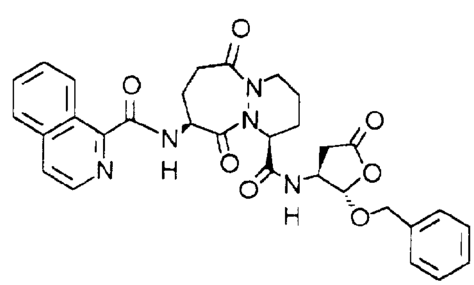
412c  ;

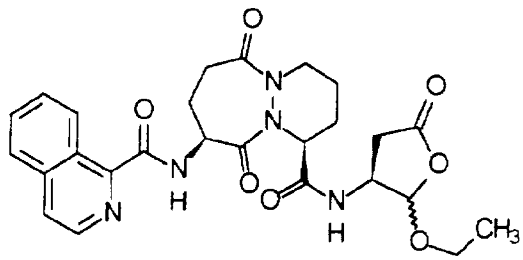
412d  ;

412e  ;

412f  ;

412g  ;

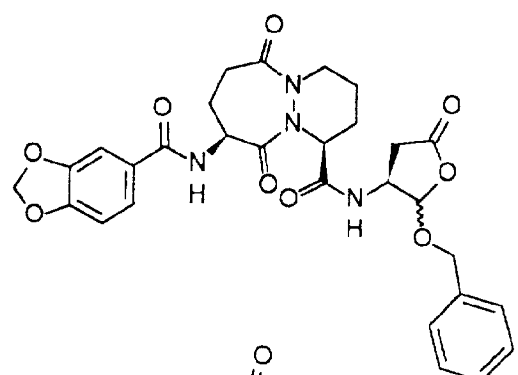
412h  ;

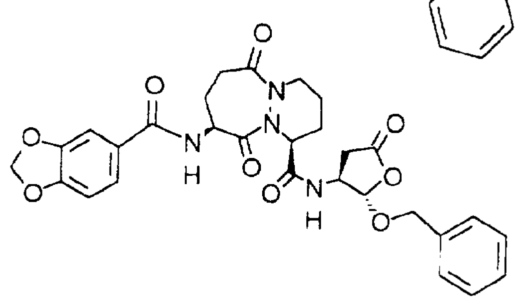
550q  .

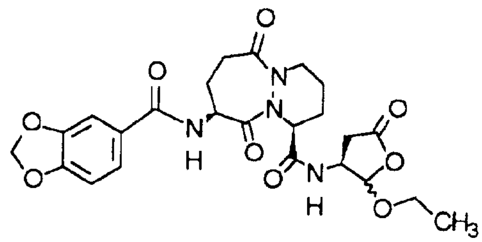
Alternatively, in this more preferred embodiment, R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is phenyl, substituted by

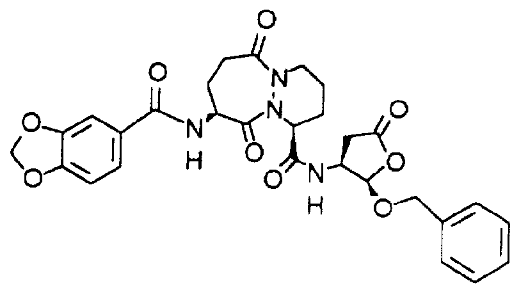
```
 O
/ \
   CH2
\ /
 O    .
```

Preferred compounds of this more preferred embodiment include, but are not limited to:

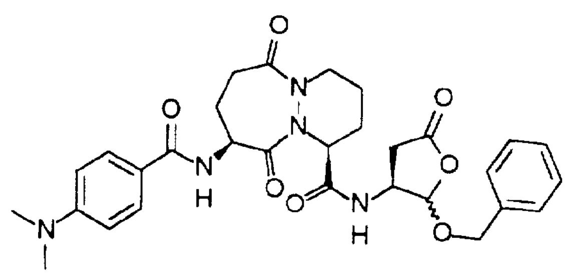
213n  ;

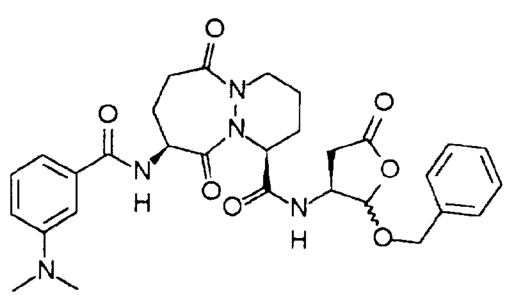
415a  ;

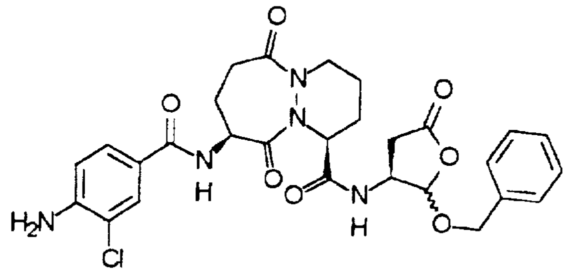
415b  ; and

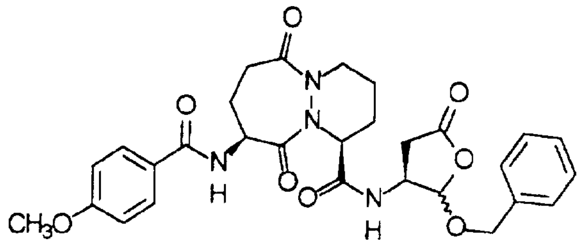
415c  .

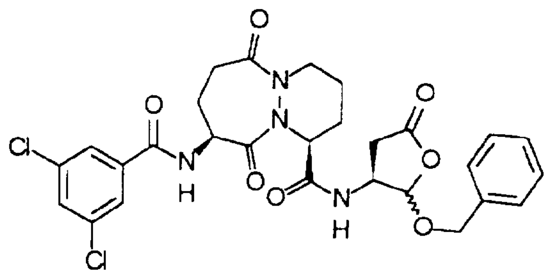
Other compounds of embodiment (K) include, but are not limited to:

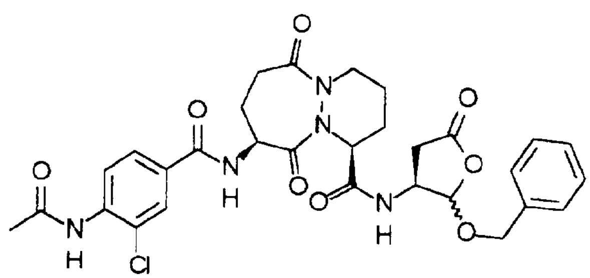
213f  ;

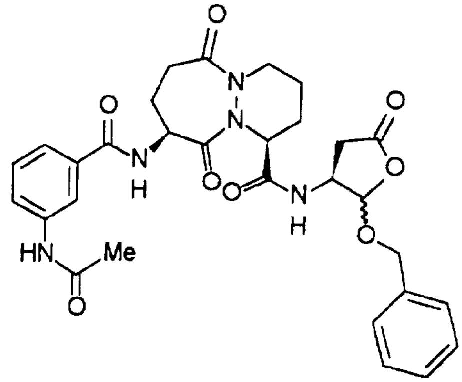
213g  ;

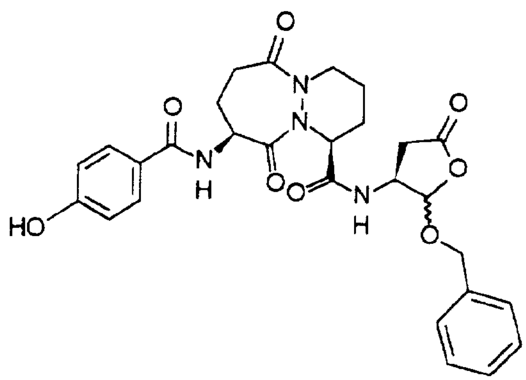
213h  ;

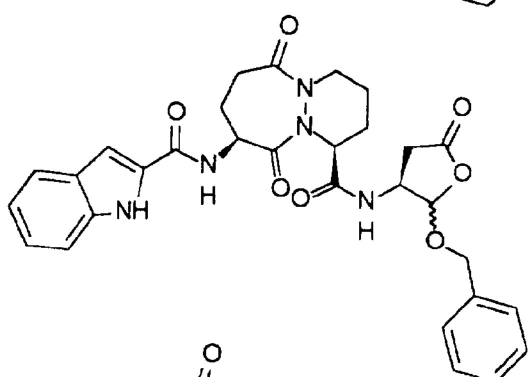
213i  ;

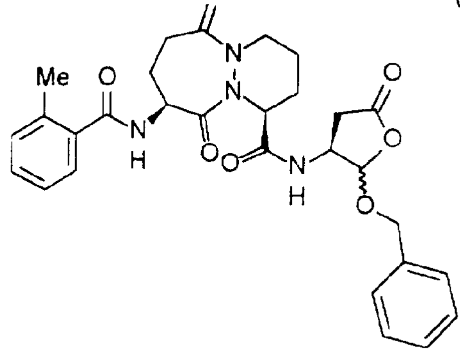
213j  ;

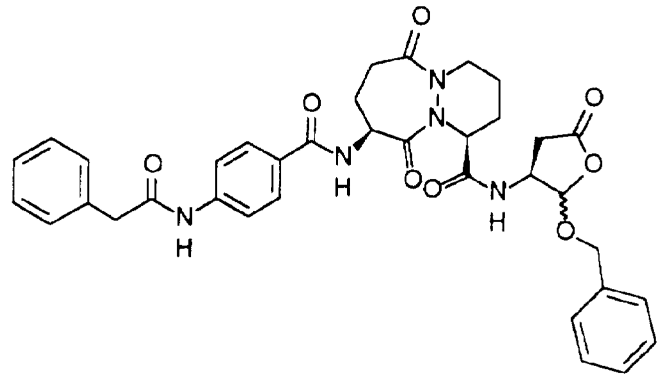
213l  ;

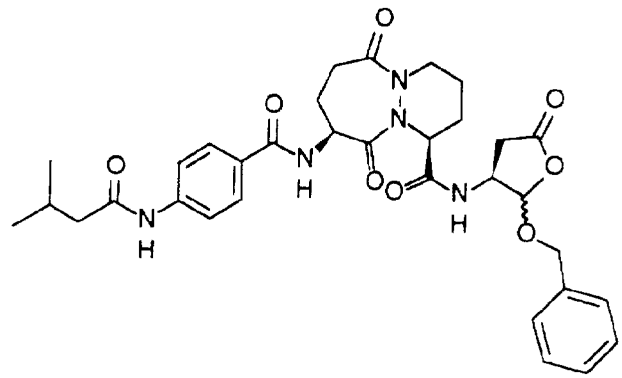
213o  ;

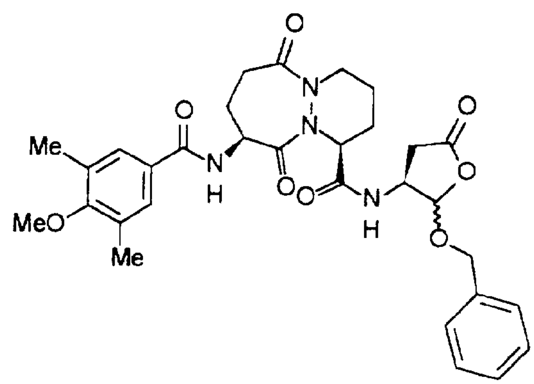
213p  ;

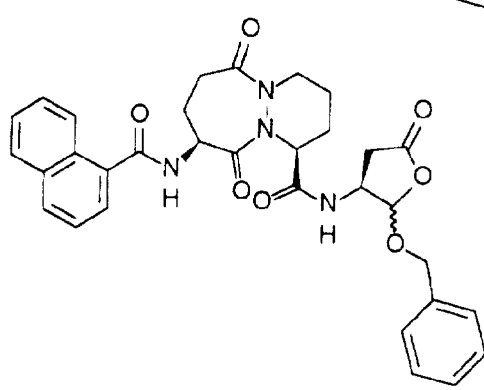
213q  ;

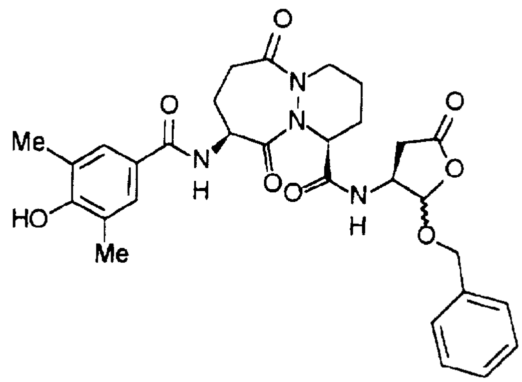
213r  ;

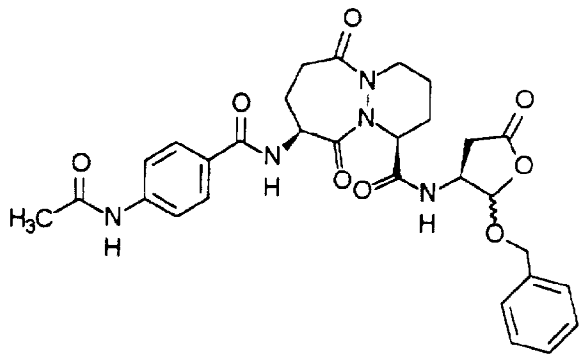
213s  ;

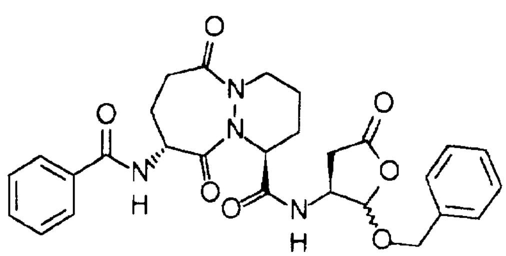
213t  ;

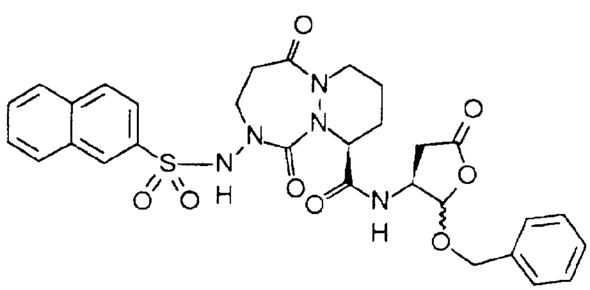
213u  ;

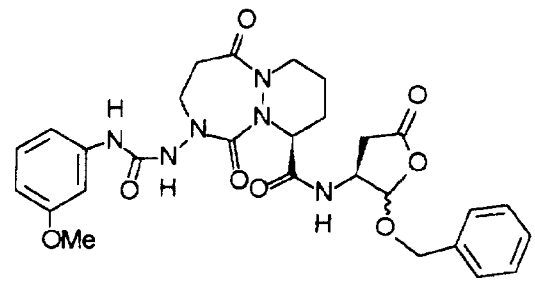
213v  ;

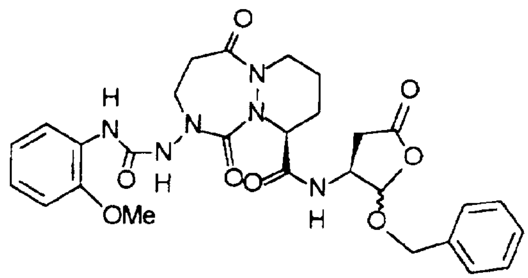
213w  ;

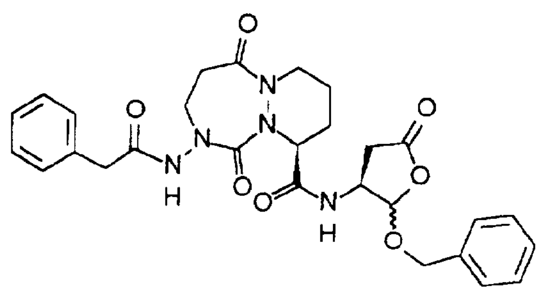
213x  ;

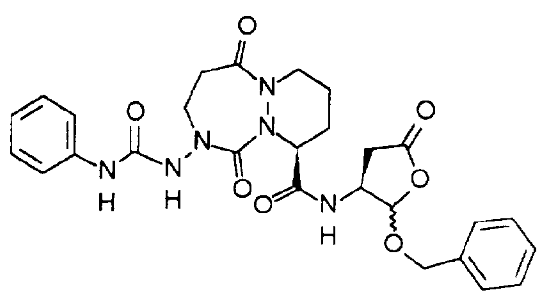
245b  ;

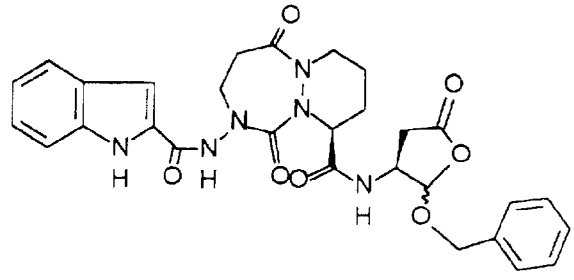
264a  ;

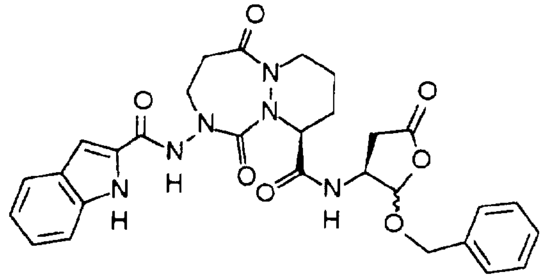
264c  ;

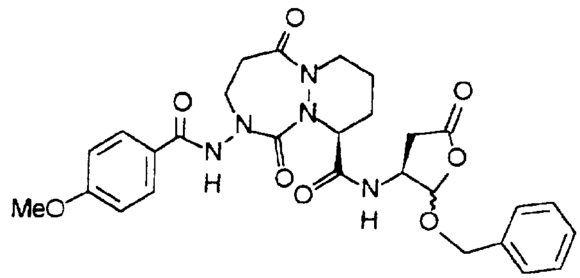
264d  ;

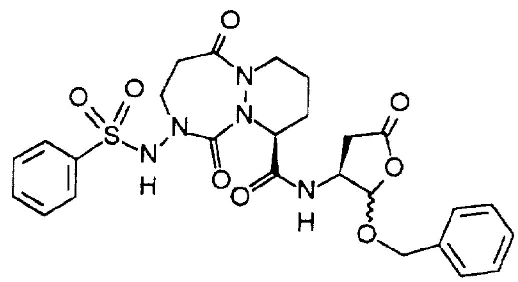
264e  ;

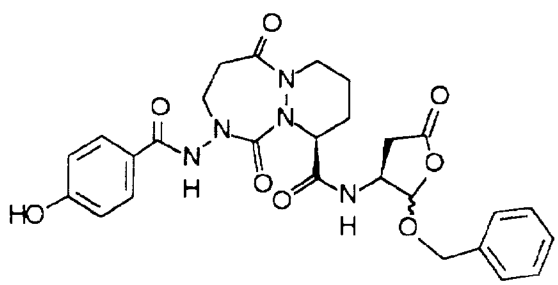
264f  ;

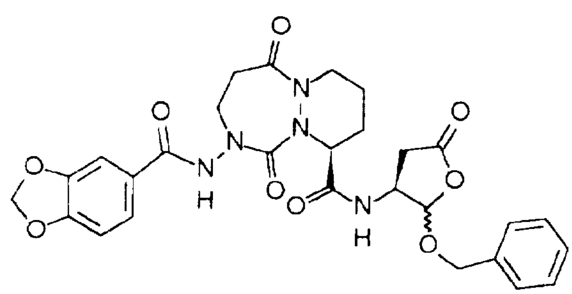
264g  ;

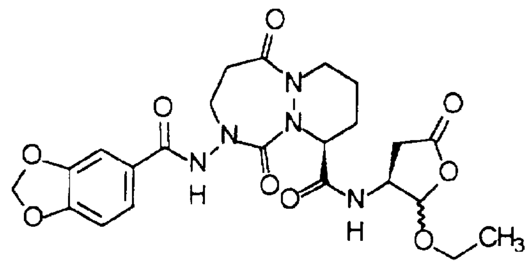
264h  ;

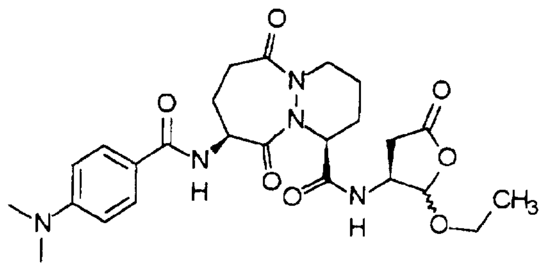
264i  ;

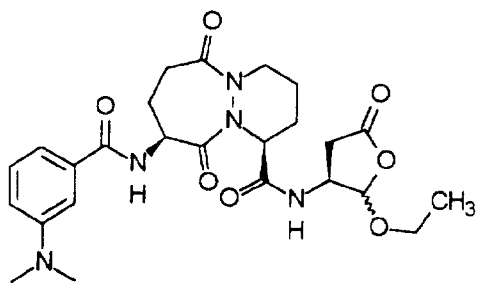
264j  ;

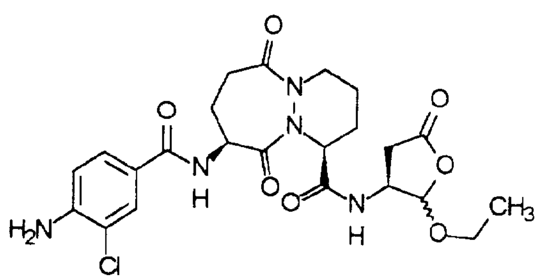
264k  ;

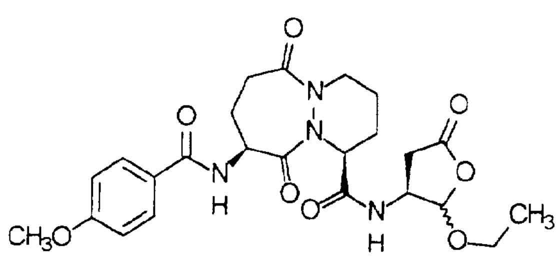
264l  ;

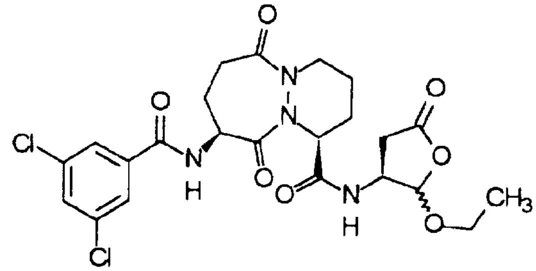
528  ;

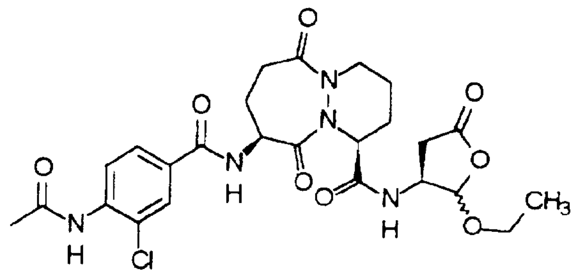
550f  ;

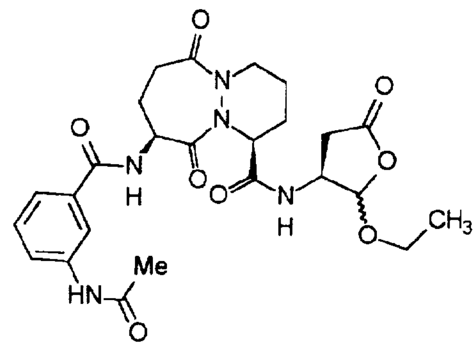
550g  ;

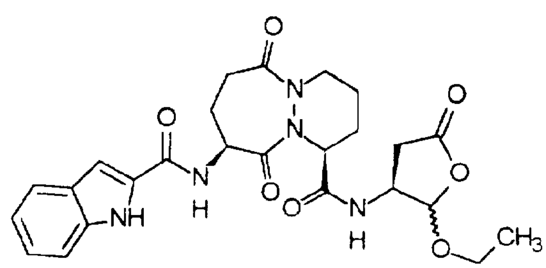
550h  ;

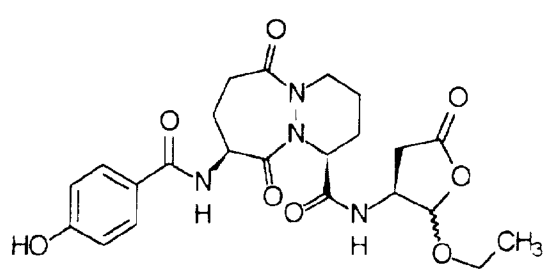
550i  ;

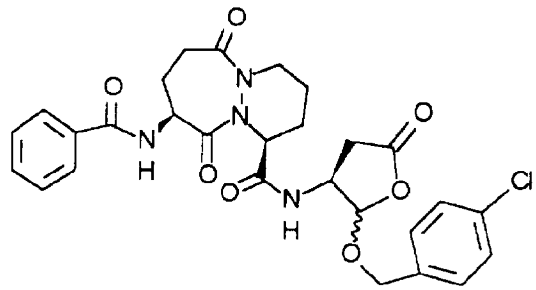
550j  ;

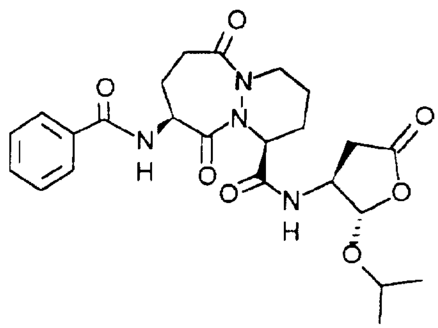
550l  ;

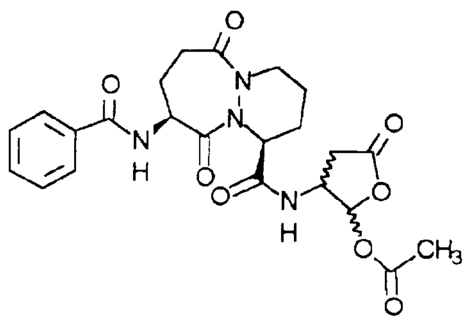
550n  ;

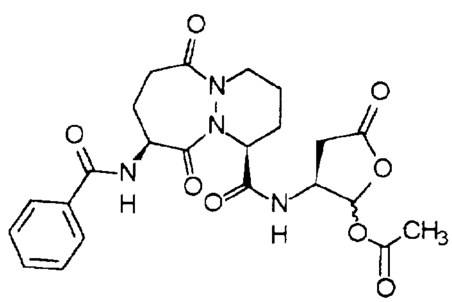
550o  ;

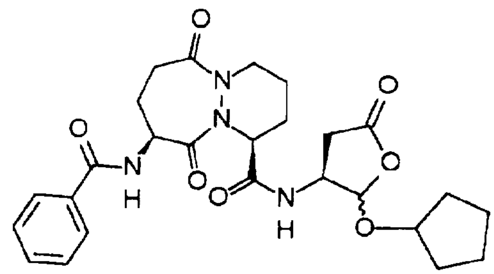
550p  ;

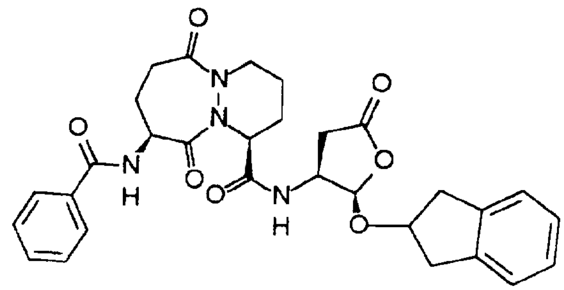
2100f  ;

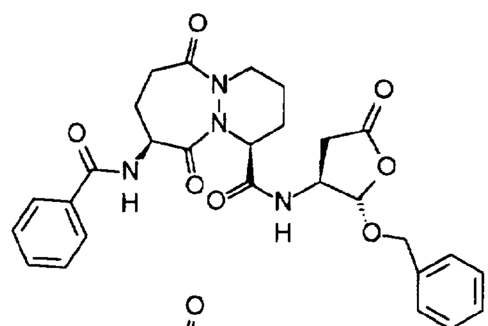
2100g  ;

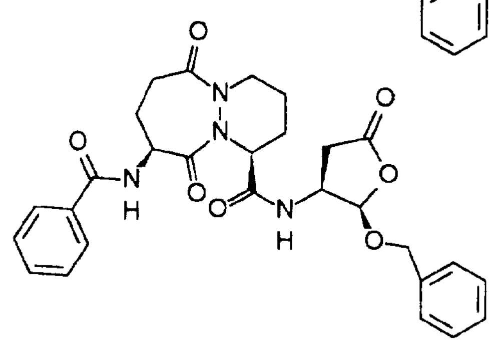
2100h  ;

2100k  ;

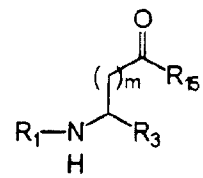
2100l  ;

2100m  ;

2100n  ;

2100o  .

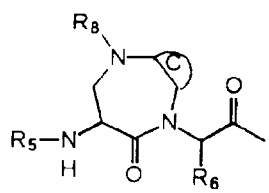
The ICE inhibitors of another embodiment (L) of this invention are those of formula :

(VII) 

wherein:

m is 1 or 2;

R_1 is selected from the group consisting of the following formulae:

(w2)  ;

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being singly or multiply substituted by $-Q_1$;

R_3 is selected from the group consisting of:

$-CN$,

$-C(O)-H$,

$-C(O)-CH_2-T_1-R_{11}$,

$-C(O)-CH_2-F$,

$-C=N-O-R_9$, and

$-CO-Ar_2$;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$-C(O)-N(R_{10})(R_{10})$
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
-H,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

$-Ar_4$,

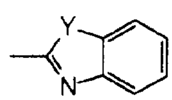
$-(CH_2)_{1-3}-Ar_4$,

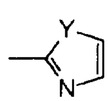
-H, and

$-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with Ar_3, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains

6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group consisting of -NH_2, -CO_2H, -Cl, -F, -Br, -I, -NO_2, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, -OR_5, -NHR_5, -OR_9, -N(R_9)(R_{10}), -R_9, -C(O)-R_{10}, and

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 O
/ \
   CH2;
\ /
 O
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provided that when -Ar_3 is substituted with a Q_1 group which comprises one or more additional -Ar_3

groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferably,

m is 1;

C is a ring chosen from the set consisting of benzo, pyrido, and thieno, the ring optionally being singly or multiply substituted by halogen, $-NH_2$, $-NH-R_5$, or $-NH-R_9$, $-OR_{10}$, or $-R_9$, wherein R_9 is a straight or branched $-C_{1-4}$ alkyl group, and R_{10} is -H or a straight or branched $-C_{1-4}$ alkyl group;

T_1 is O or S;

R_6 is H;

R_{11} is selected from the group consisting of $-Ar_4$, $-(CH_2)_{1-3}-Ar_4$, and $-C(O)-Ar_4$;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl,

naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
    O
   / \
      CH2,
   \ /
    O
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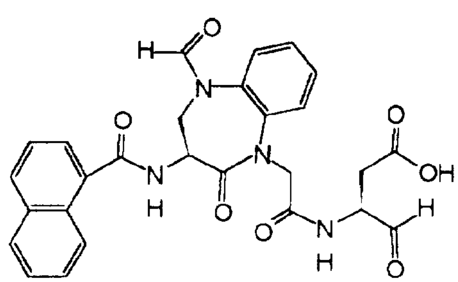
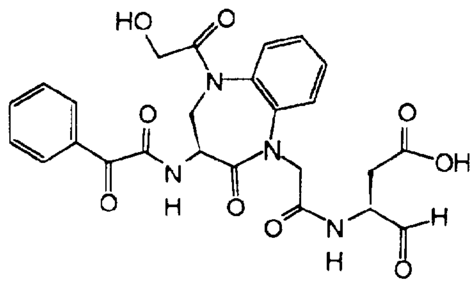
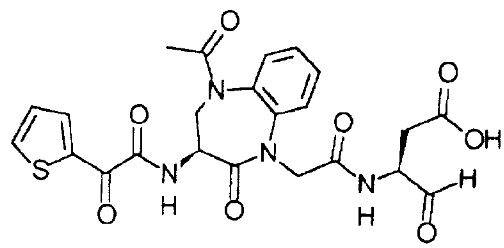
wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

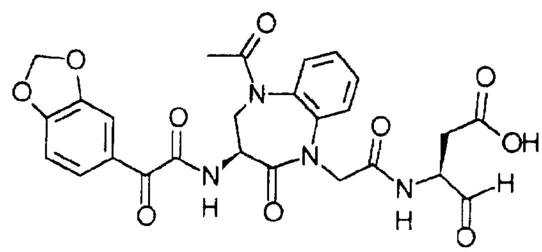
provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

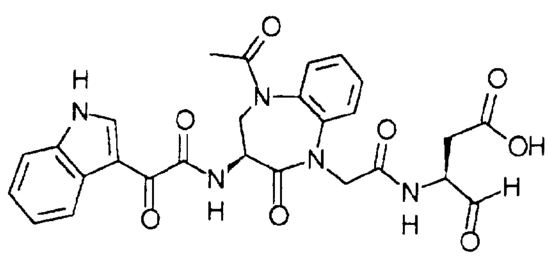
Preferred compounds of this preferred embodiment include, but are not limited to:

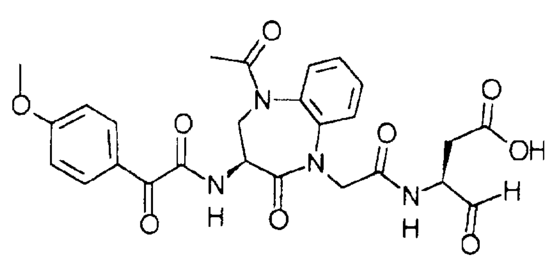
653  ;

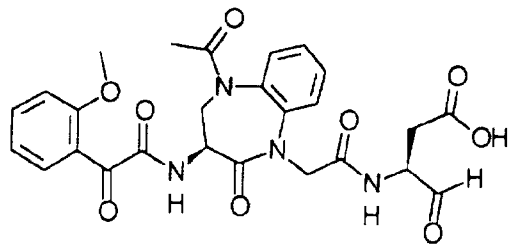
681  ;

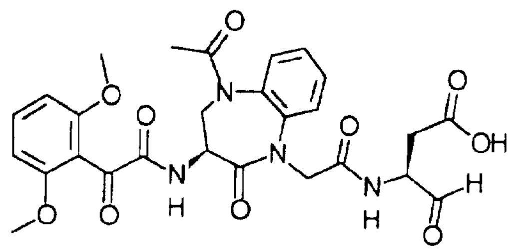
701  ;

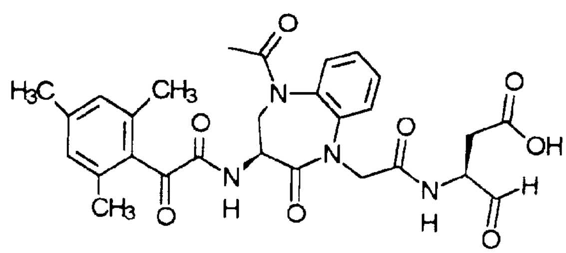
702  ;

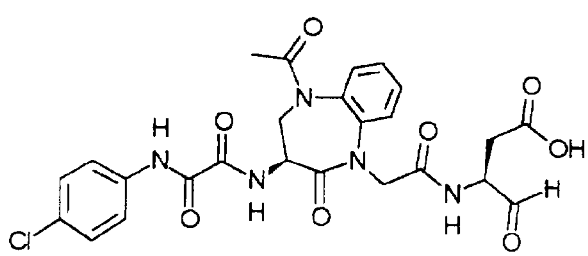
703  ;

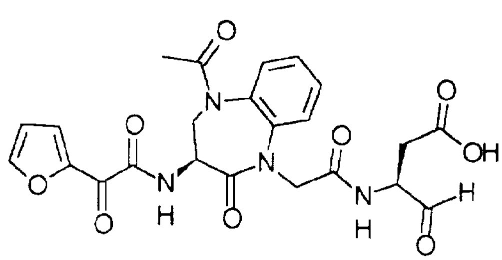
704  ;

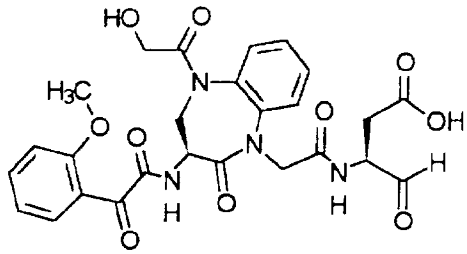
705  ;

706  ;

709  ;

710  ;

711  ; and

921 

More preferably, R_3 is -C(O)-Ar_2 and the other substituents are as described above.

Alternatively, R_3 is -C(O)CH_2-T_1-R_{11};

Alternatively, R_3 is -C(O)-H.

Preferably, in any of the above compounds of embodiment (L), R_8 is selected from the group consisting of:

-C(O)-R_{10},

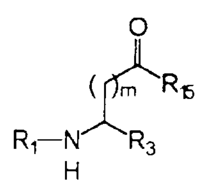
-C(O)O-R_9,

-C(O)-CH_2-OR_{10}, and

-C(O)-CH_2C(O)-R_9.

More preferably, R_8 is -C(O)-CH_2-OR_{10} and R_{10} is -H or -CH_3.

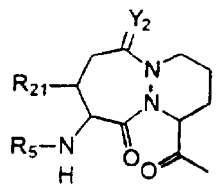
Alternatively, ICE inhibitors of embodiment (L) of this invention are those of formula :

(V) 

wherein:

m is 1;

R_1 is:

(e10-B)  ;

R_3 is selected from the group consisting of:

$-CN$,

$-C(O)-H$,

$-C(O)-CH_2-T_1-R_{11}$,

$-C(O)-CH_2-F$,

$-C{=}N-O-R_9$, and

$-CO-Ar_2$;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$-C(O)-N(R_{10})(R_{10})$

$-S(O)_2-R_9$,

$-S(C)_2-NH-R_{10}$,

$-C(O)-CH_2-O-R_9$,

$-C(O)C(O)-R_{10}$,

$-R_9$,

$-H$,

$-C(O)C(O)-OR_{10}$, and

$-C(O)C(O)-N(R_9)(R_{10})$;

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O- or -S-;

each R_9 is independently selected from the group

consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

$-Ar_4$,

$-(CH_2)_{1-3}-Ar_4$,

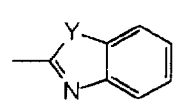
-H, and

$-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

R_{21} is -H or $-CH_3$;

Ar_2 is:

(hh)  ,

wherein Y is O;

each Ar_3 is a cyclic group independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,

isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

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   O
  / \
     CH2,
  \ /
   O
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provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$;

provided that when:

m is 1;
R_{15} is -OH;
R_{21} is -H; and

Y_2 is O and R_3 is -C(O)-H, then R_5 cannot be: $-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic

group is phenyl, unsubstituted by $-Q_1$, 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

-H;

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl, 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$, wherein R_9 is isobutyl or $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl;

and when R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl or 5-(1-(4-chloro-2-pyridinyl)-3-trifluoromethyl)pyrazolyl, then R_5 cannot be:

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl;

and when R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, or

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methyl)phenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benztriazolyl, N-carboethoxy-5-benztriazolyl, N-carboethoxy-5-benzimidazolyl, or

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$,; and when

Y_2 is H_2, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl.

Preferably, in any of the above compounds of embodiment (L), R_3 is $-C(O)-H$ and R_5 is $-C(O)-R_{10}$ or $-C(O)-C(O)-R_{10}$ and the other substituents are as defined above.

More preferably R_{10} is $-Ar_3$ and the other substituents are as defined above.

More preferably in these more preferred compounds:

R_5 is $-C(O)-R_{10}$ and R_{10} is Ar_3, wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

$-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group;

-F,

-Cl,

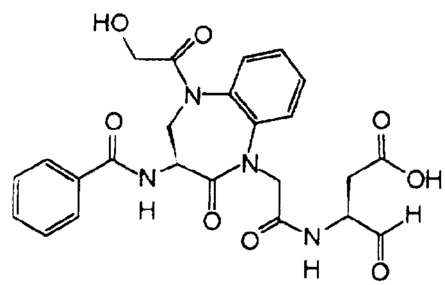
$-N(H)-R_5$, wherein $-R_5$ is -H or $-C(O)-R_{10}$,

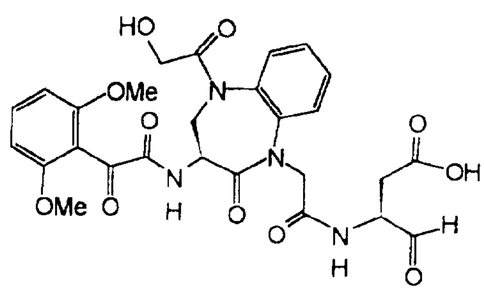
wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3, wherein Ar_3 is phenyl,

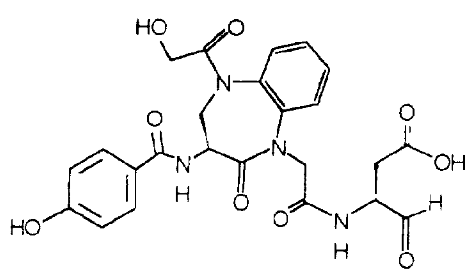
$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a $-C_{1-4}$ straight or branched alkyl group, or

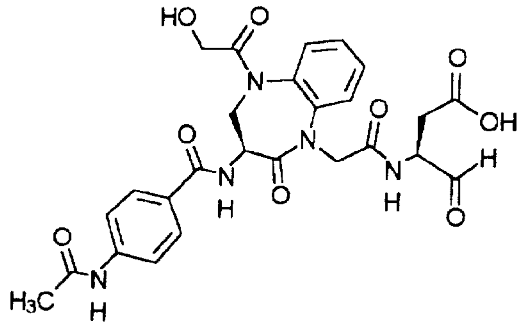
$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or branched alkyl group.

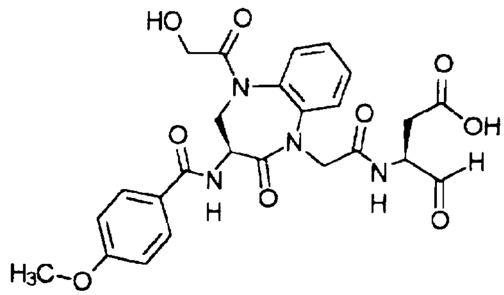
Preferred compounds of this preferred embodiment include, but are not limited to:

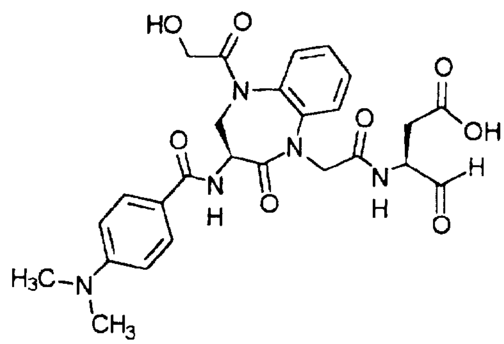
668  ;

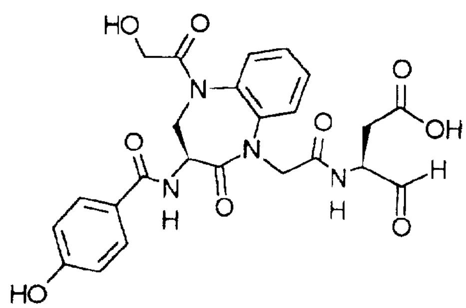
678  ;

691b  ;

911  ;

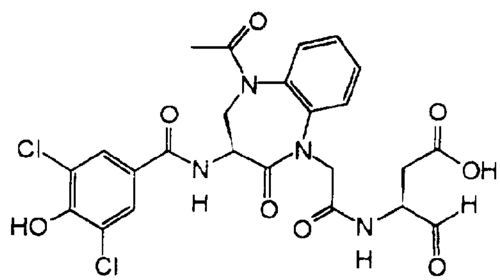
912  ;

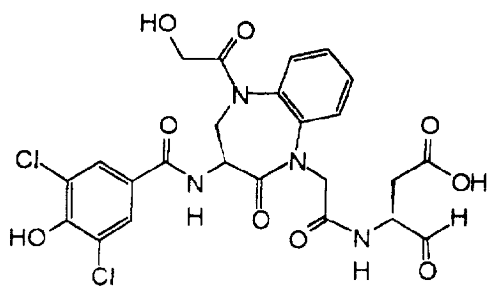
913  ; and

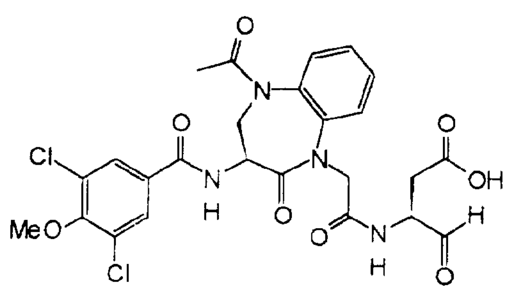
916  .

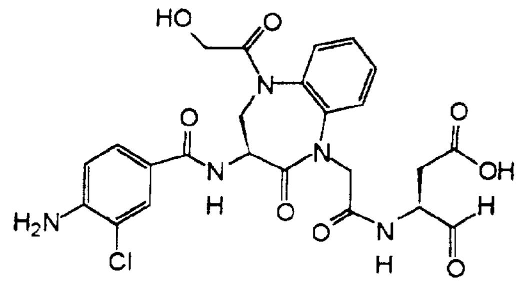
Most preferably, Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by $-NH-R_5$, $-N(R_9)(R_{10})$, or $-O-R_5$.

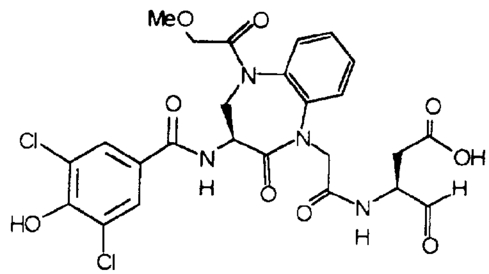
Preferred compounds of this most preferred embodiment include, but are not limited to:

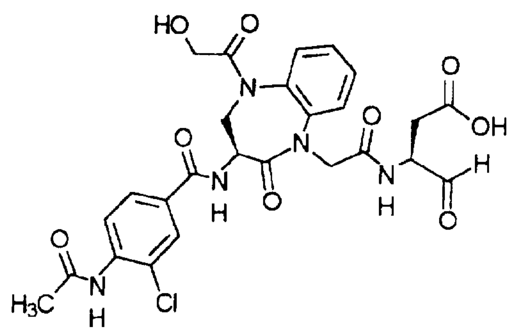
656  ;

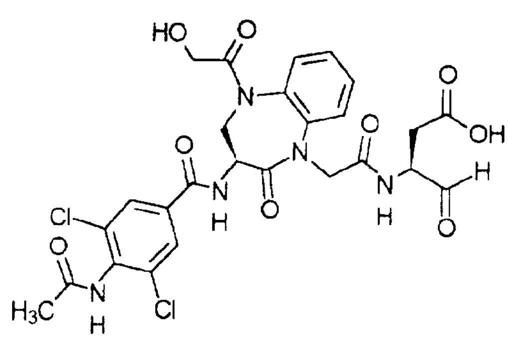
662  ;

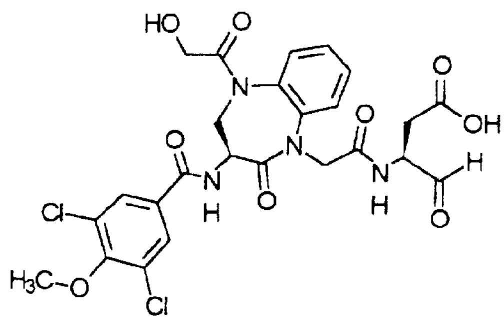
669  ;

686  ;

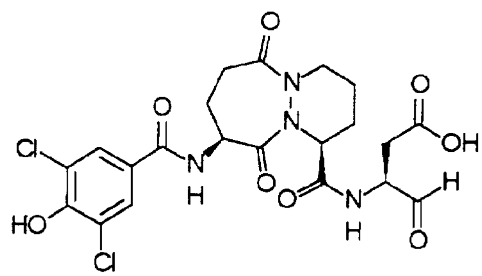
689a  ;

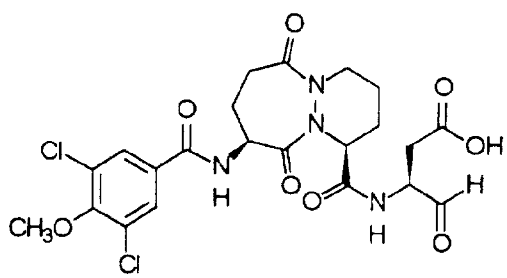
914  ;

915  ; and

918 

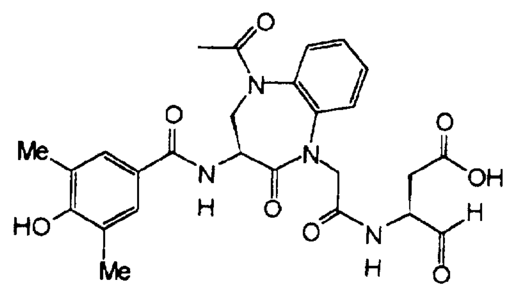
Other preferred compounds of this most preferred embodiment include, but are not limited to:

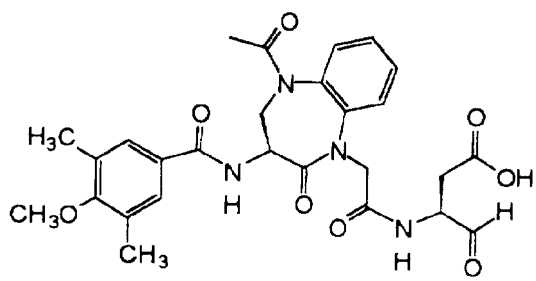
214k  ; and

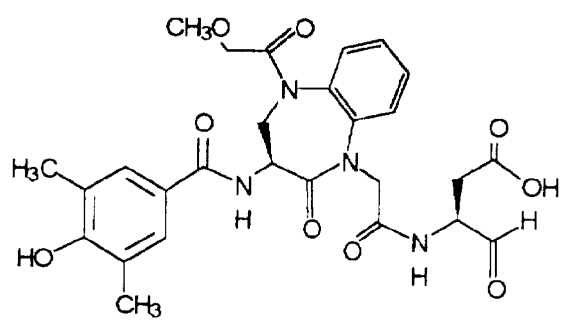
214m 

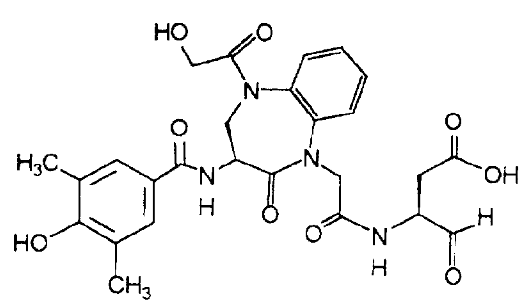
Alternatively, Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by $-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group; and at the 4-position by $-O-R_5$.

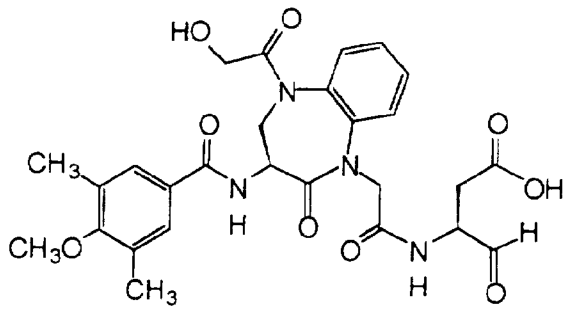
Preferred compounds of this most preferred embodiment include, but are not limited to:

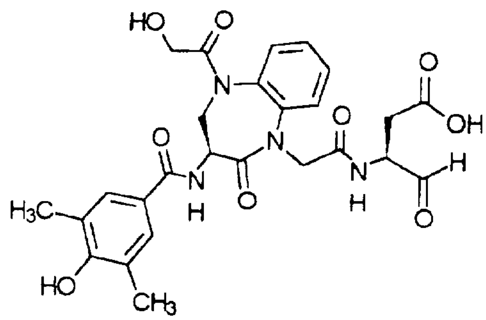
671  ;

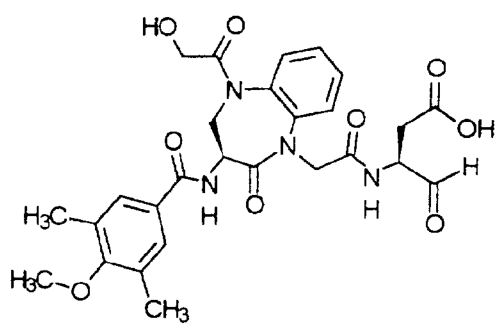
684  ;

689b  ;

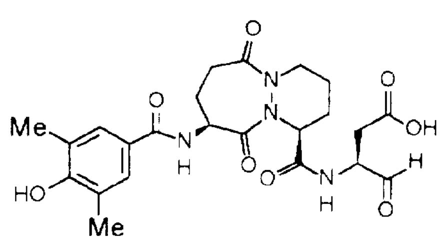
691a  ;

694  ;

917  ; and

922  .

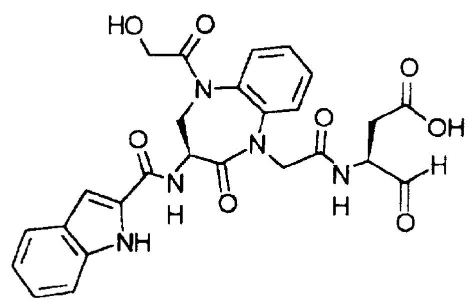
Another preferred compound of this most preferred embodiment includes, but is not limited to:

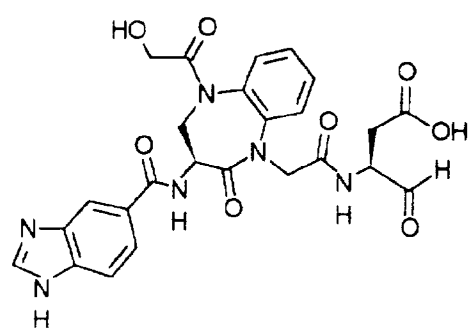
214w  .

Alternatively, in this more preferred embodiment:

R_5 is -C(O)-R_{10}, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q_1.

Preferred compounds of this more preferred embodiment include, but are not limited to:

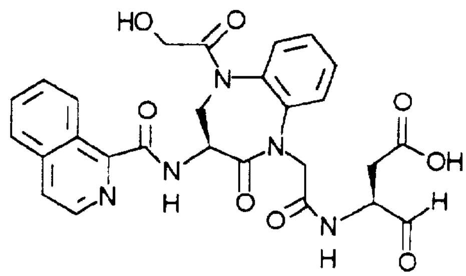
919  ; and

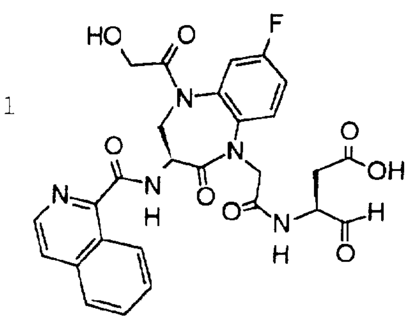
920  .

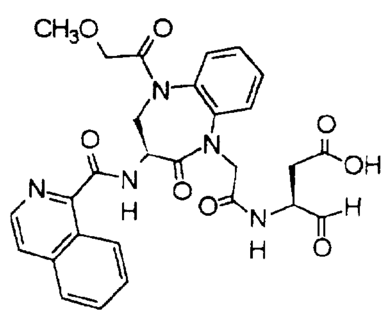
Most preferably, the Ar_3 cyclic group is isoquinolyl, and said cyclic group optionally being singly or multiply substituted by -Q_1.

A preferred compound of this most preferred embodiment includes, but is not limited

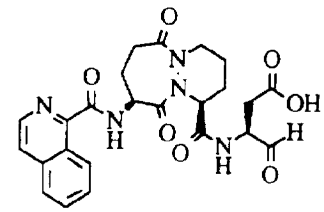
to:

696  ;

696-1  ; and

699  .

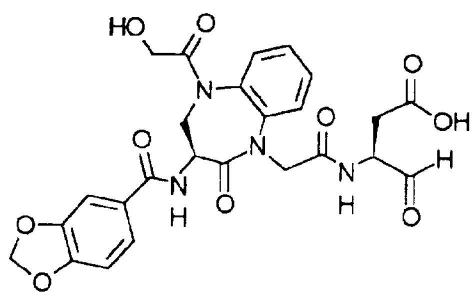
Another preferred compound of this most preferred embodiment includes, but is not limited to:

412  .

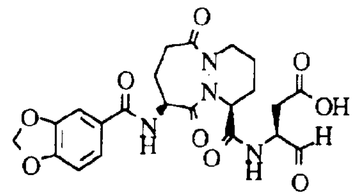
Alternatively, in this more preferred embodiment R_5 is -C(O)-R_{10}, wherein R_{10} is -Ar_3 and the Ar_3 cyclic group is phenyl, substituted by

```
 O
/ \
   CH2
\ /
 O   .
```

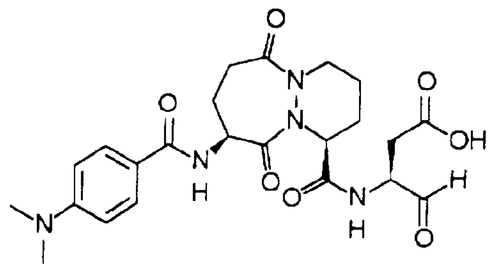
A preferred compound of this more preferred embodiment includes, but is not limited to:

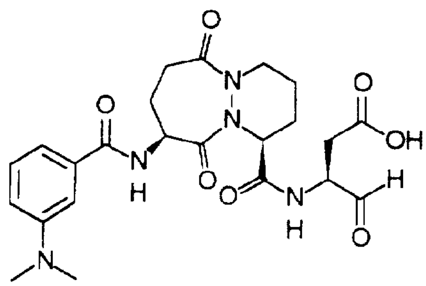
910  .

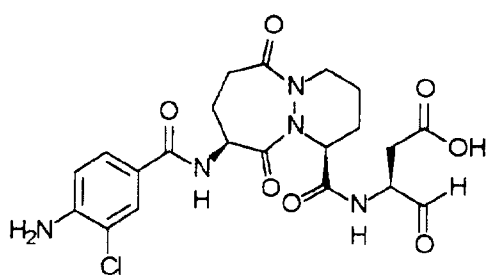
A preferred compound of this more preferred embodiment includes, but is not limited to:

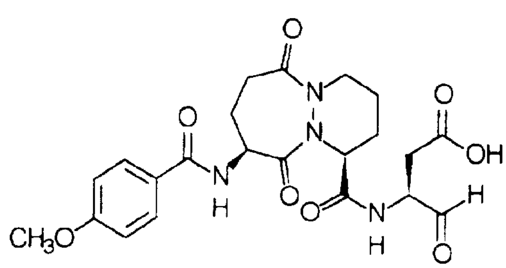
415  .

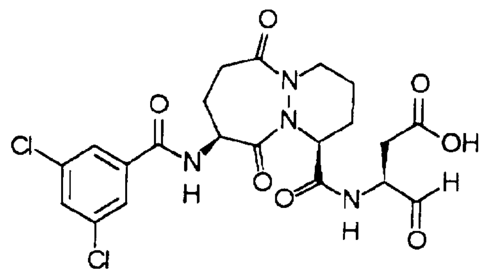
Other compounds of embodiment (L) include, but are not limited to:

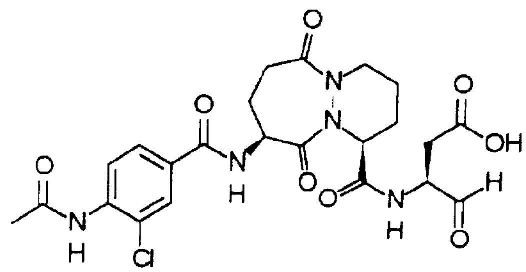
214f  ;

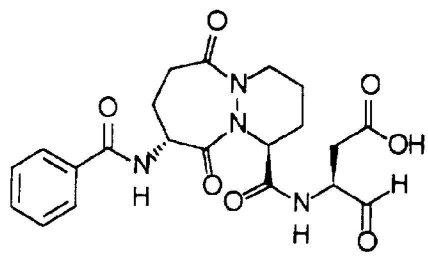
214g  ;

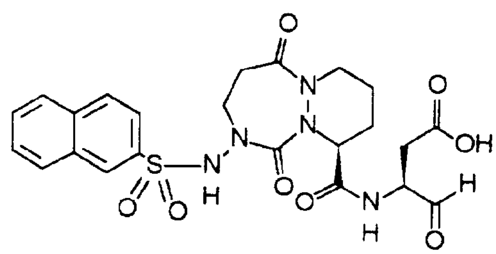
214h  ;

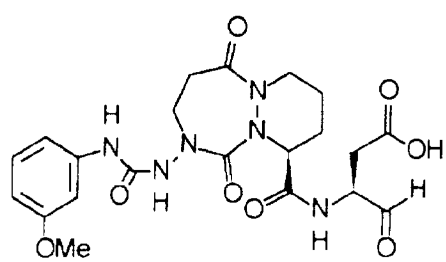
214i  ;

214j  ;

214l  ;

246b  ;

265a  ;

265c  ;

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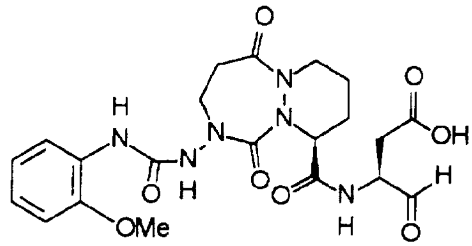

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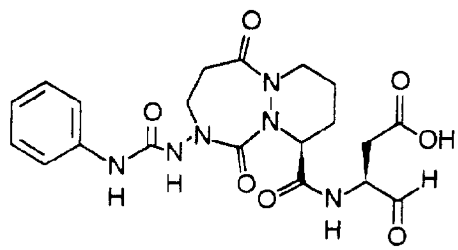

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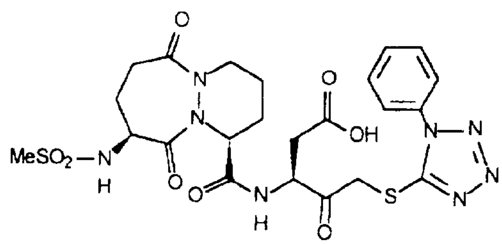

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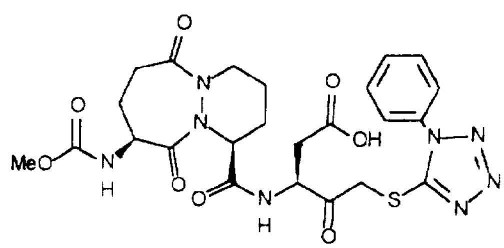

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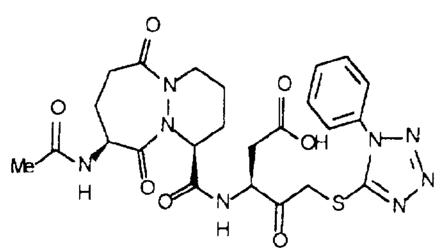

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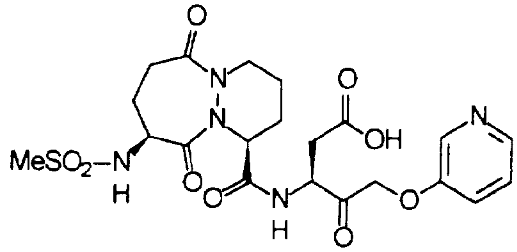
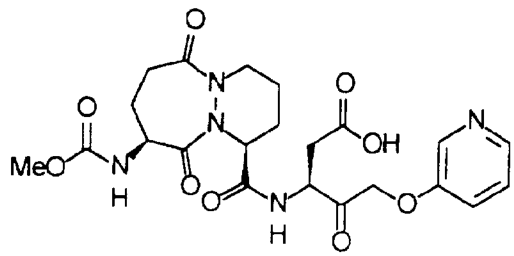
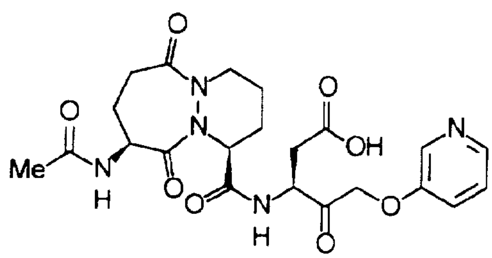
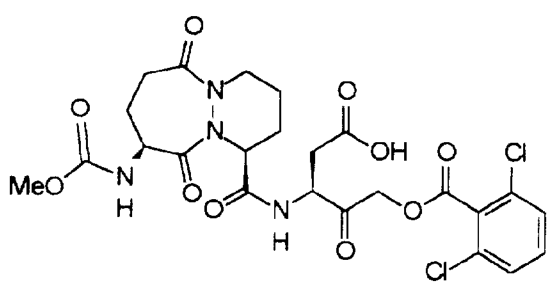
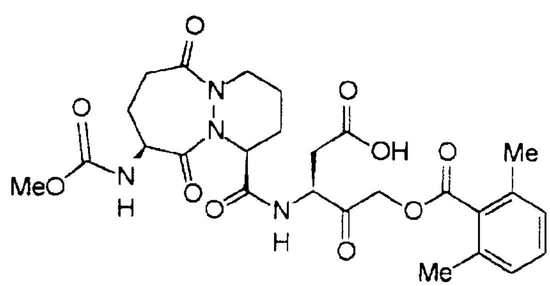
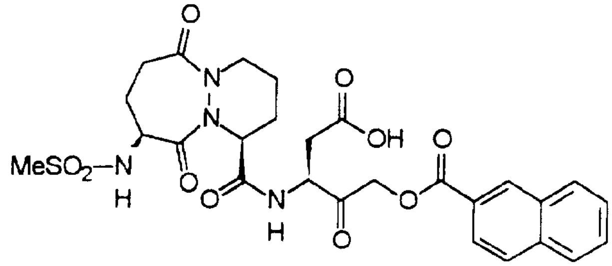
283b  ;

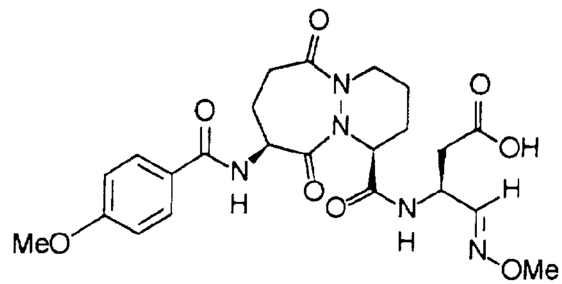
283c  ;

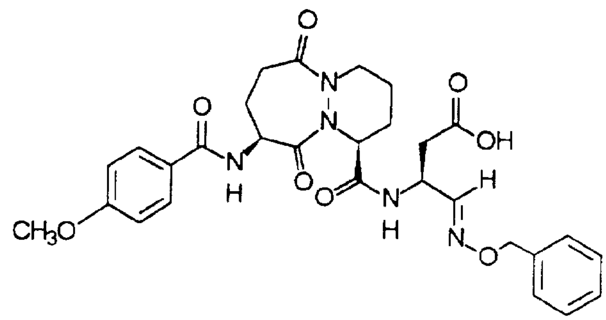
283d  ;

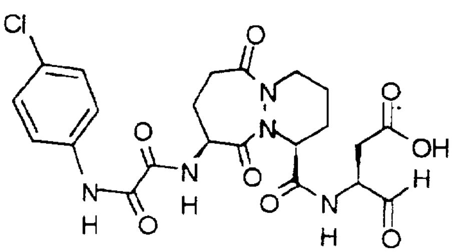
284  ;

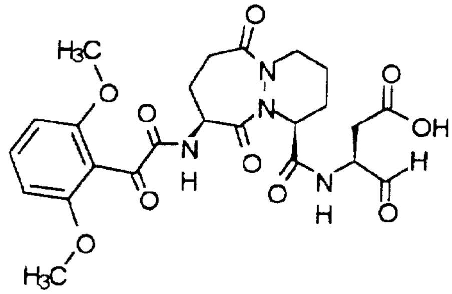
285  ;

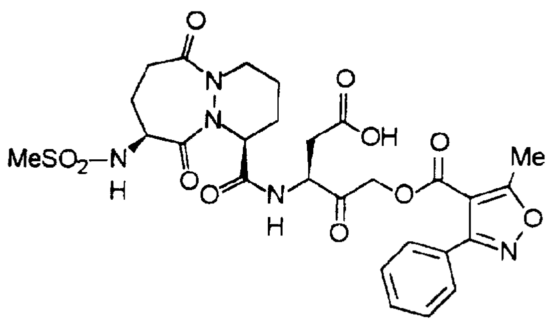
286  ;

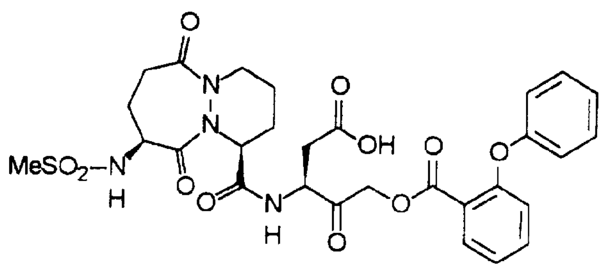
308c  ;

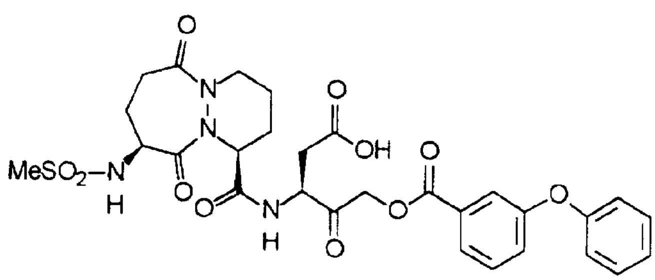
308d  ;

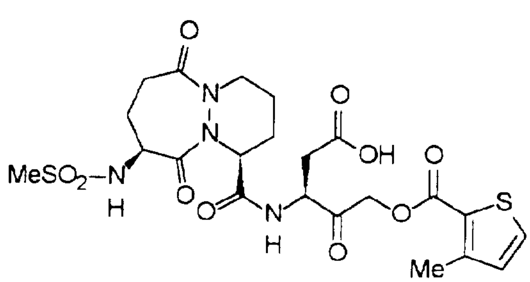
500  ;

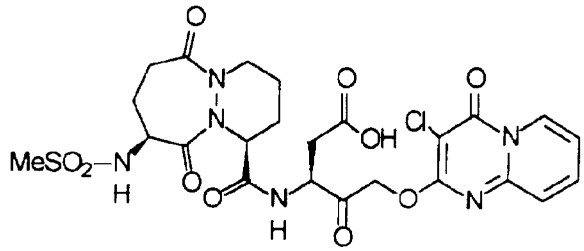
501  ;

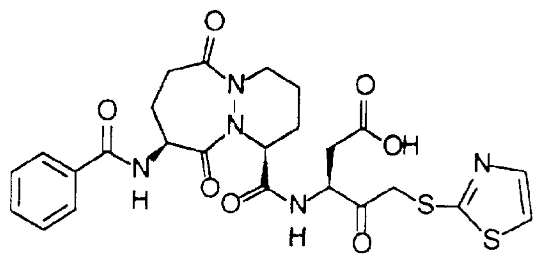
505b  ;

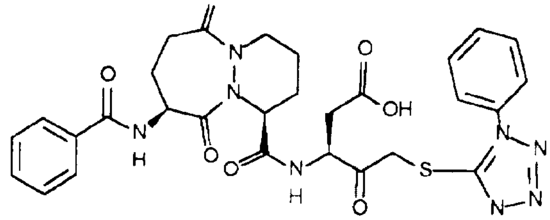
505c  ;

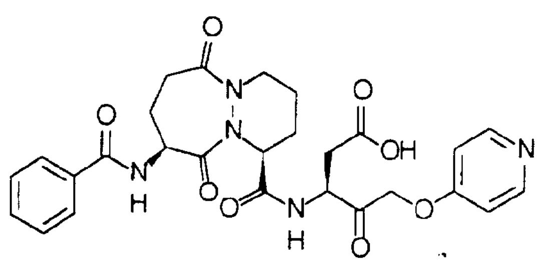
505d  ;

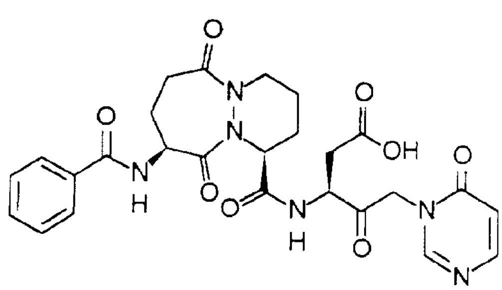
505e  ;

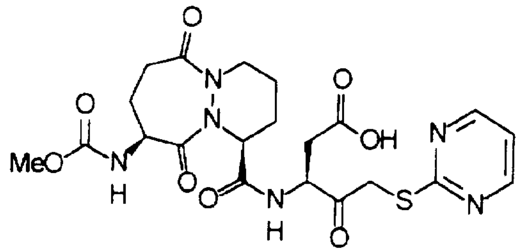
505f  ;

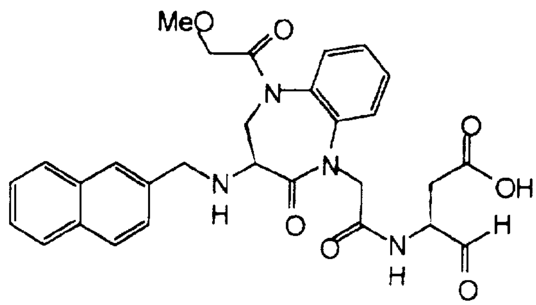
510a  ;

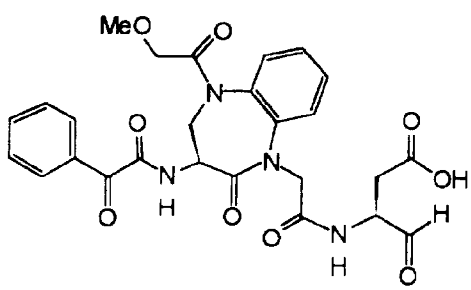
510b  ;

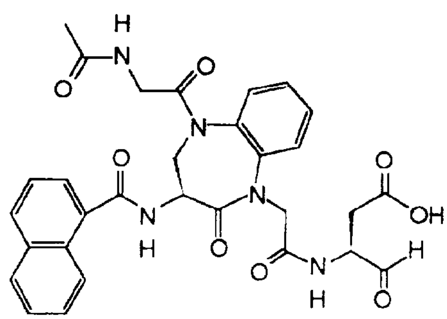
510c  ;

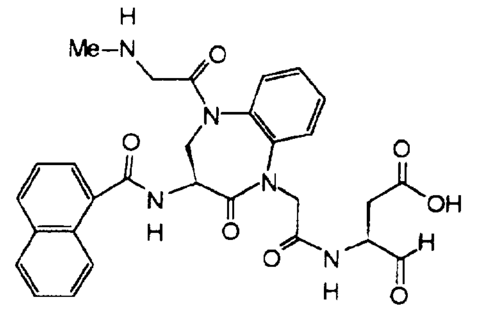
510d  ;

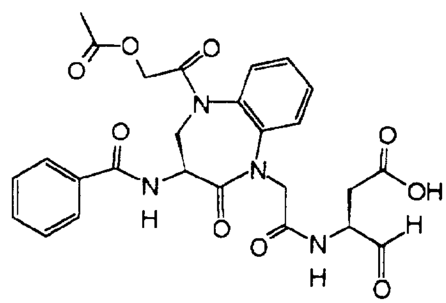
511c  ;

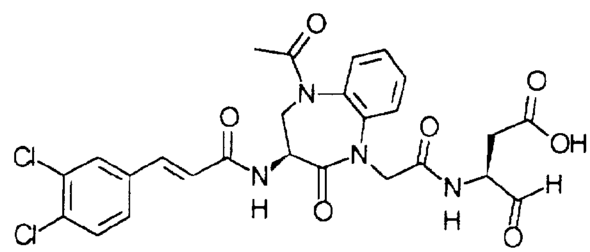
640  ;

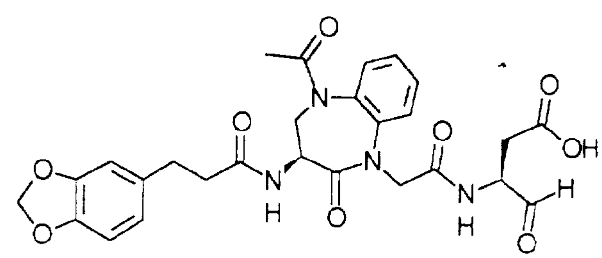
642  ;

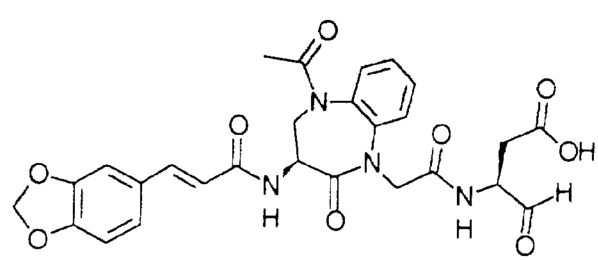
645  ;

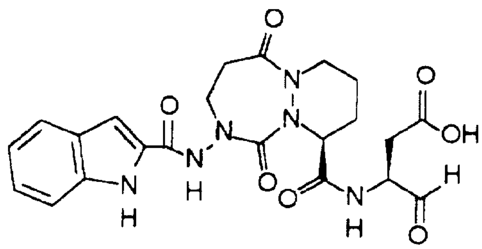
650  ;

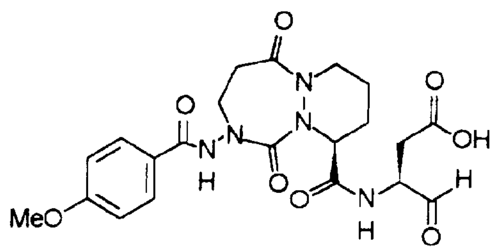
683  ;

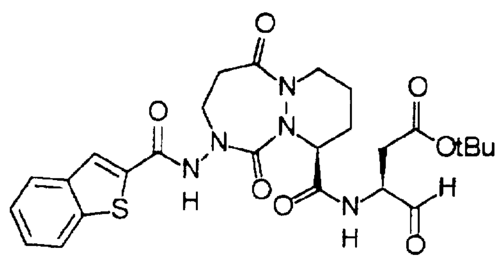
700  ;

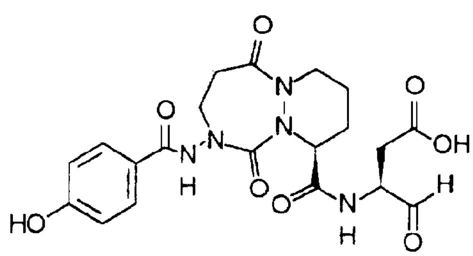
707  ;

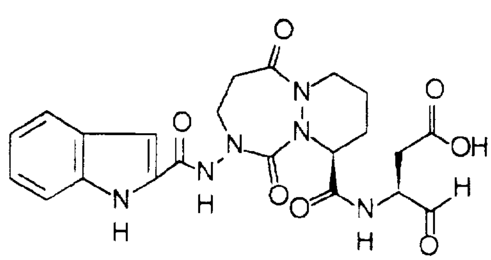
708  ;

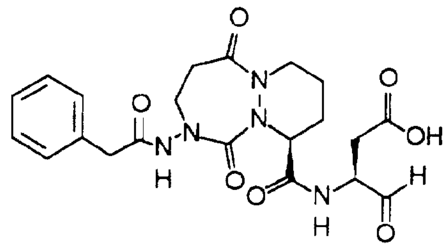
1018  ;

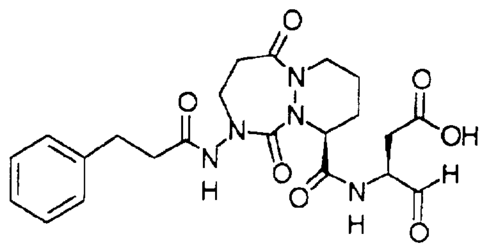
1052  ;

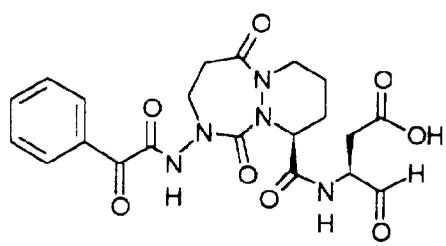
1053  ;

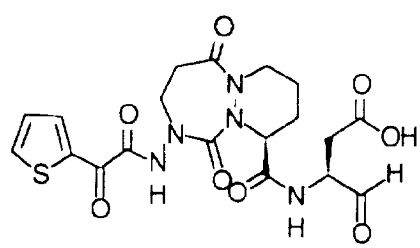
1056  ;

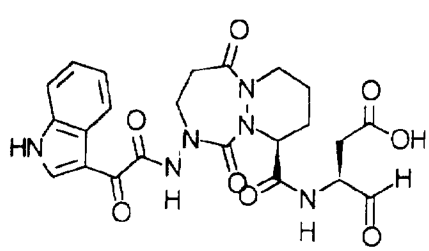
1075  ;

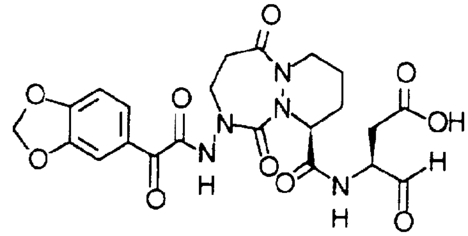
1095  ;

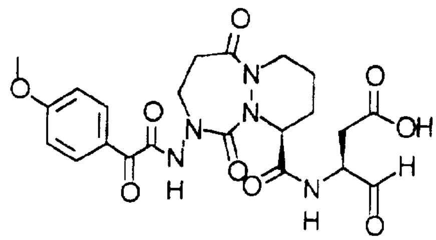
1105  ;

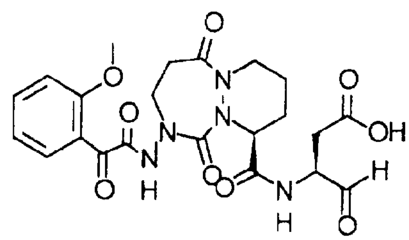
1106  ;

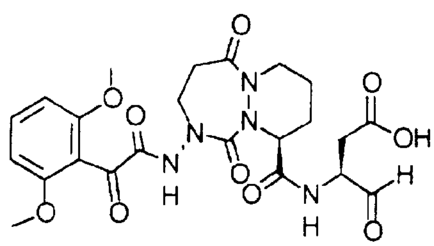
1107  ;

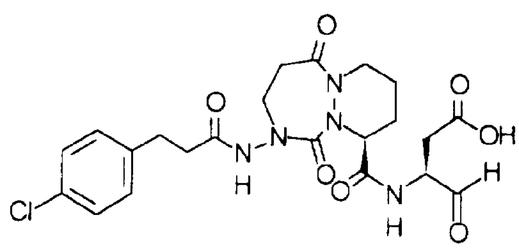
1108  ;

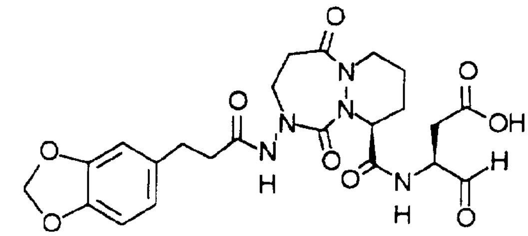
1109  ;

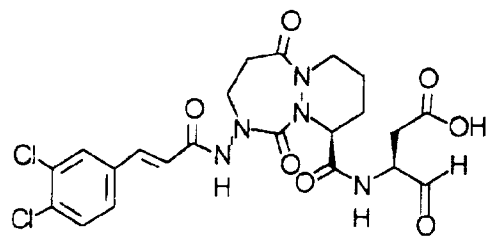
1110  ;

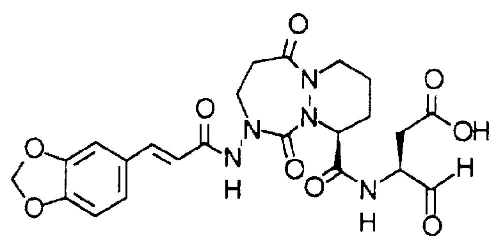
1111  ;

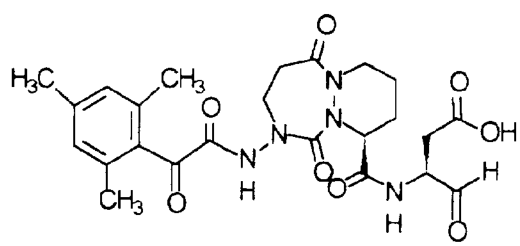
1112  ;

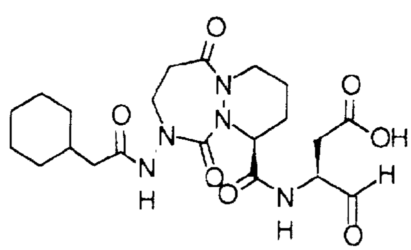
1113  ;

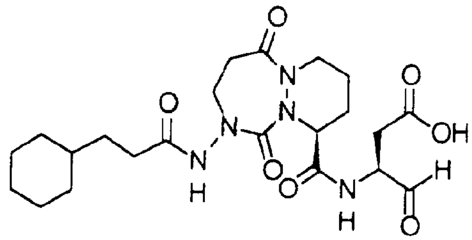
1114  ;

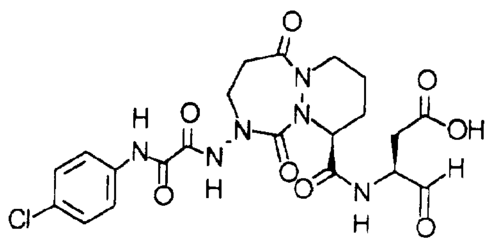
1115  ;

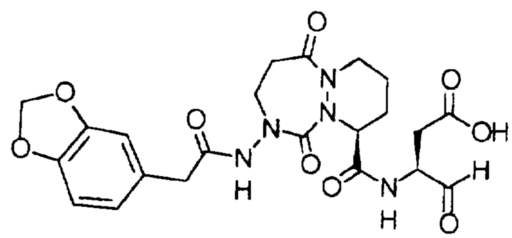
1116  ;

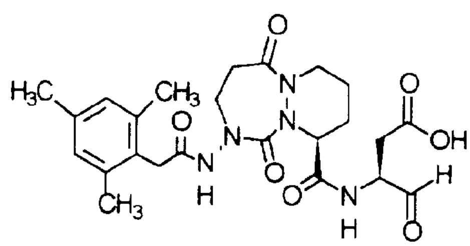
1117  ;

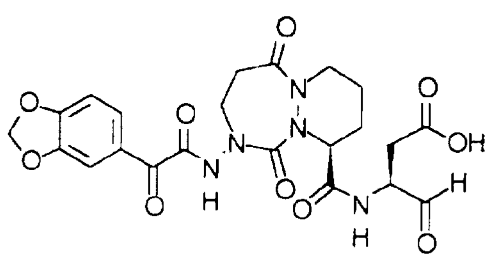
1118  ;

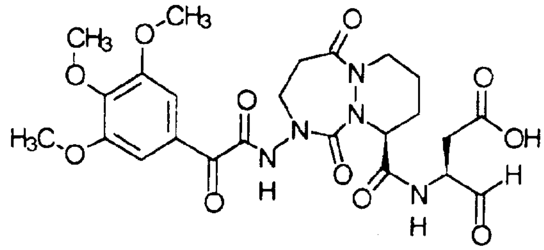
1119  ;

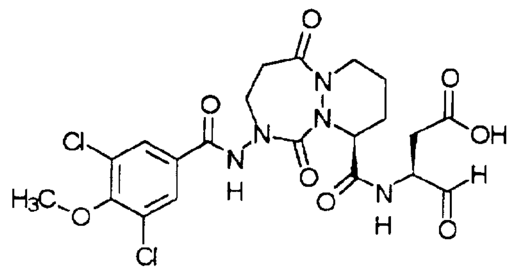
1120  ;

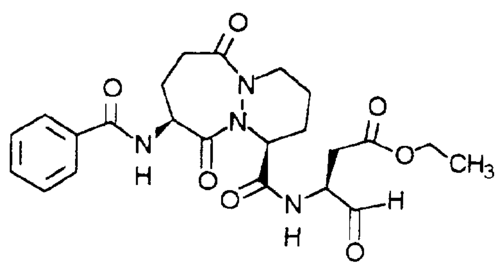
1121  ;

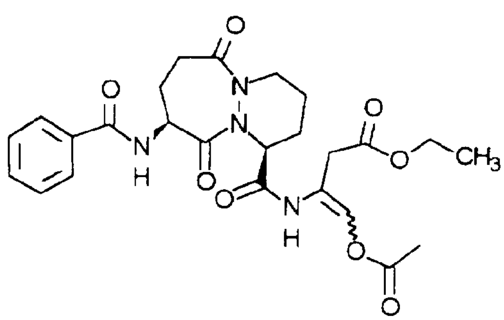
1122  ;

1123  ;

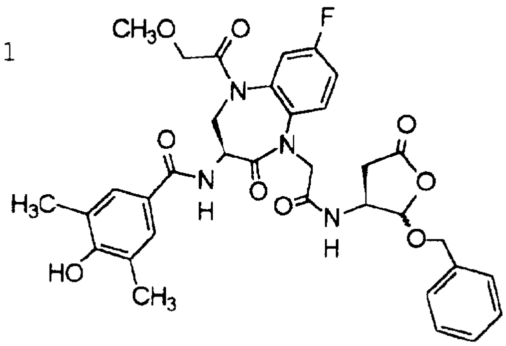
1124  ;

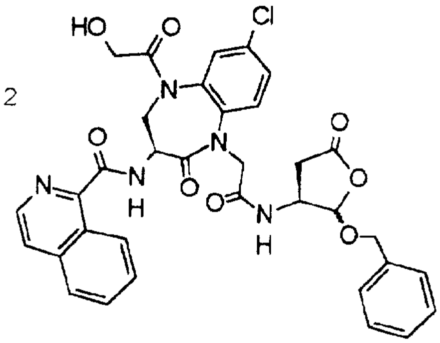
1125  ;

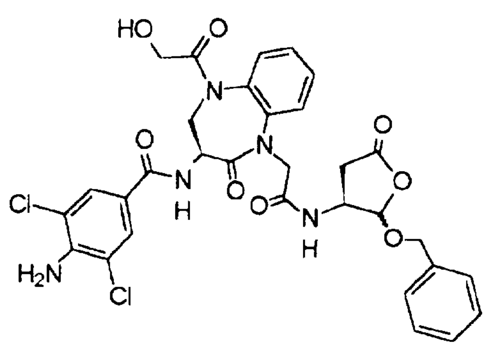
2100i  ;

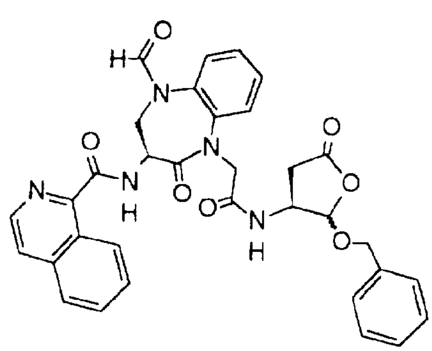
2100j  .

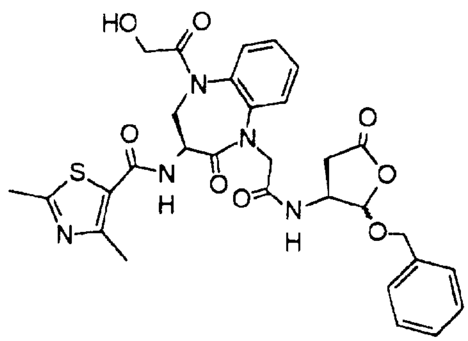
Other compounds of embodiment (K) include, but are not limited to:

688b-1  ;

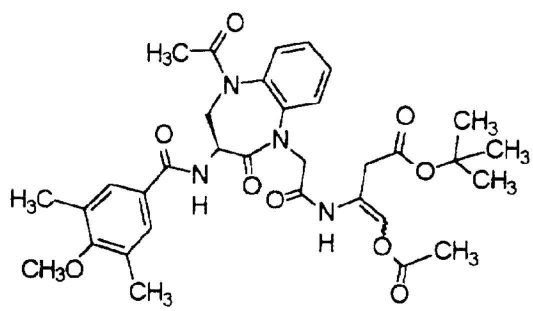
696a-2  ;

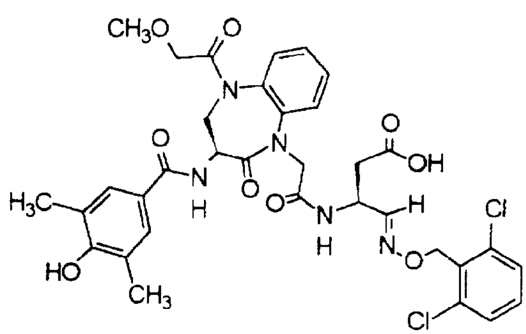
697a  ;

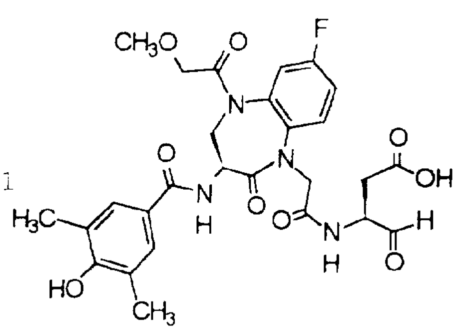
698a  ;

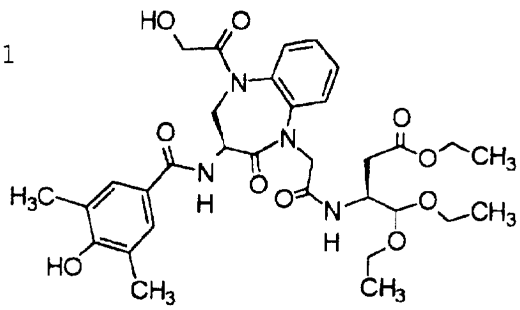
800  .

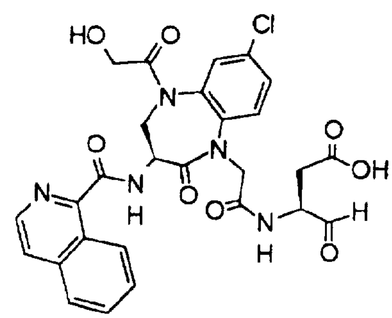
Other compounds of embodiment (L) include, but are not limited to:

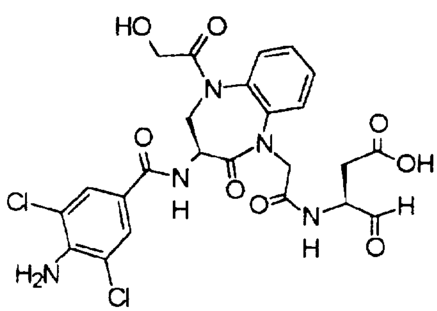
684a  ;

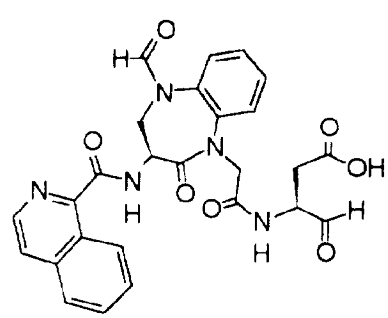
688c  ;

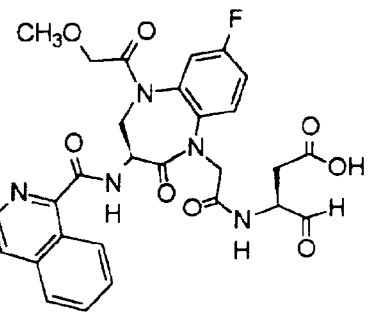
689b-1  ;

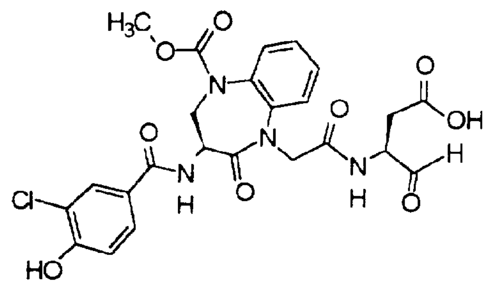
690a-1  ;

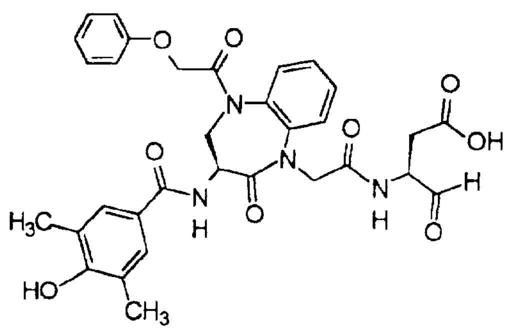
696-2  ;

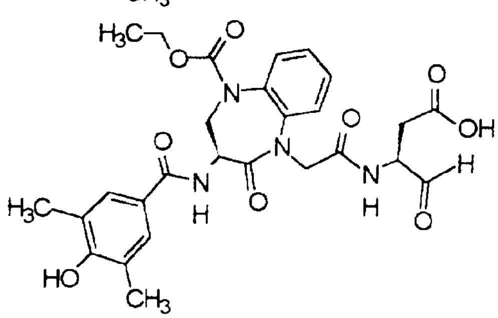
697  ;

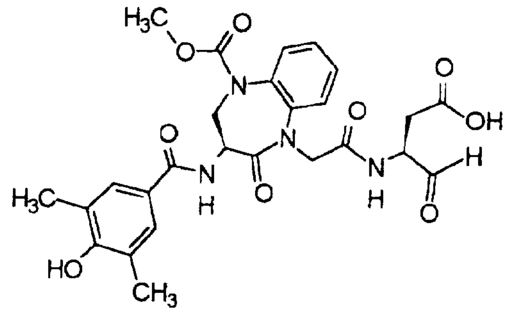
698  ;

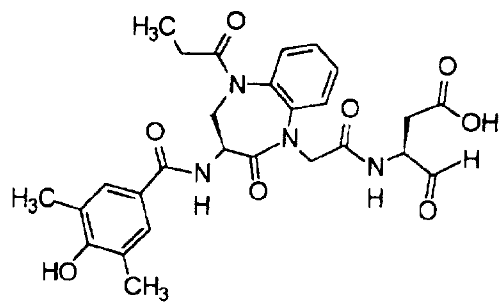
699a-2  ;

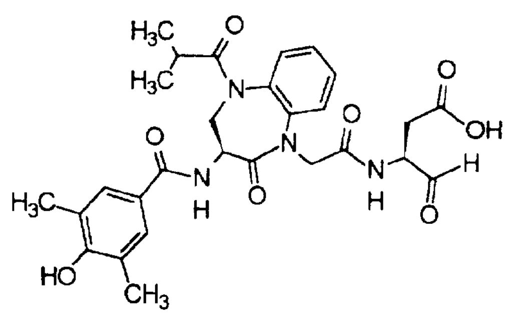
720  ;

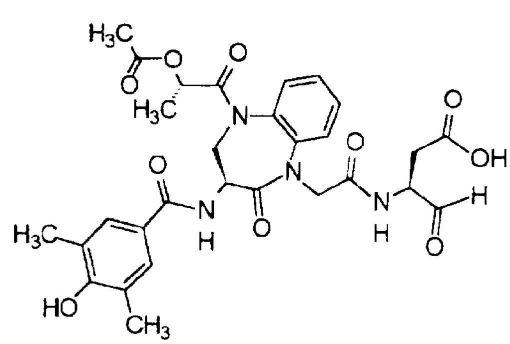
721  ;

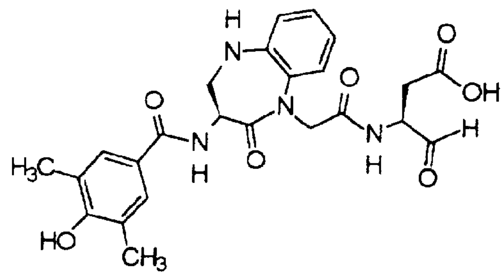
722  ;

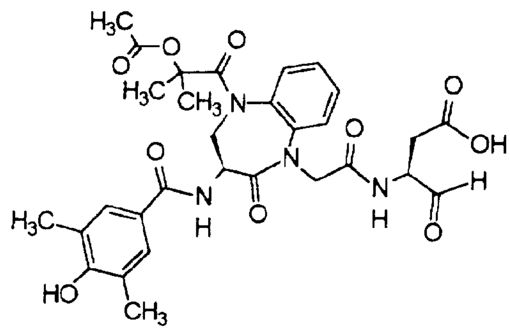
723  ;

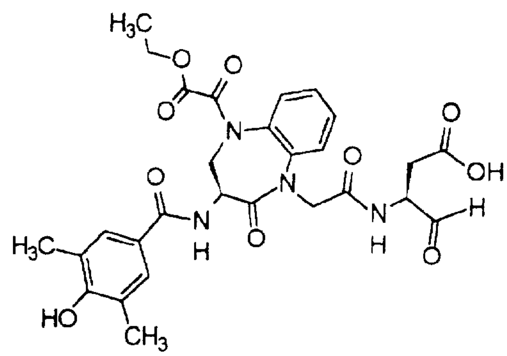
724  ;

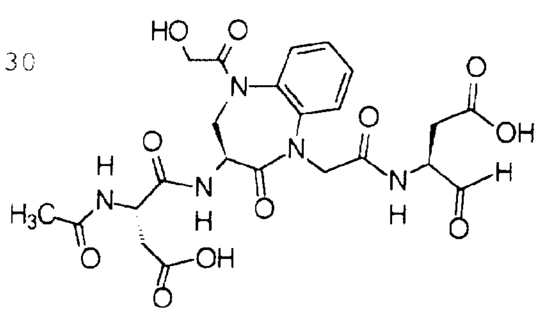
725  ;

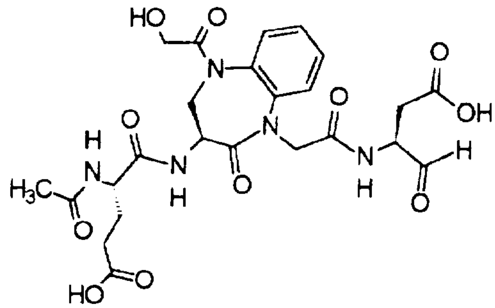
726  ;

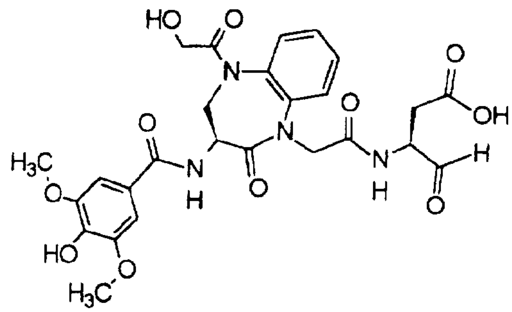
727  ;

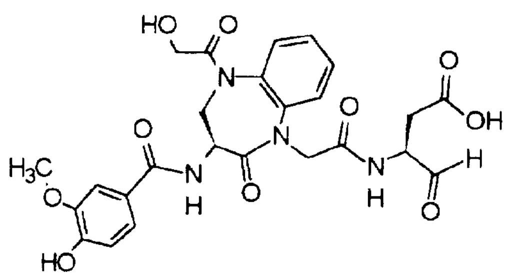
728  ;

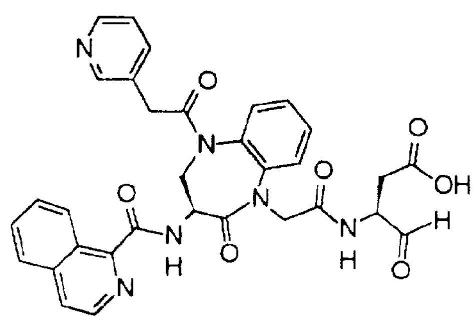
729  ;

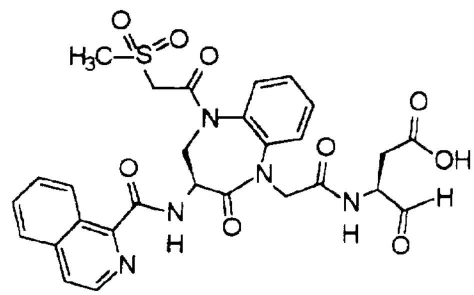
730  ;

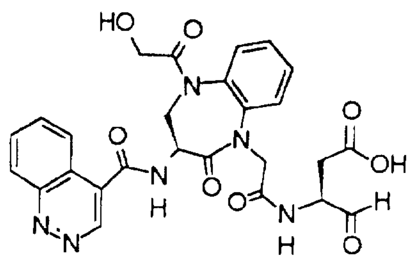
731  ;

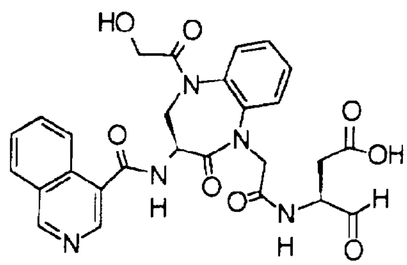
732  ;

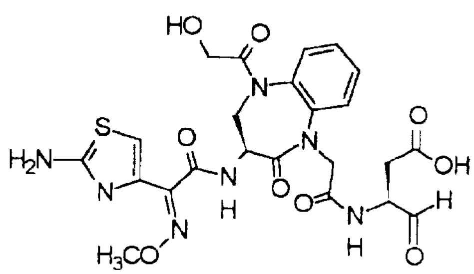
733  ;

734  ;

735  ;

736  ;

737  ;

738  ;

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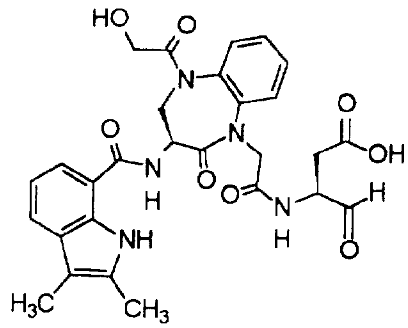

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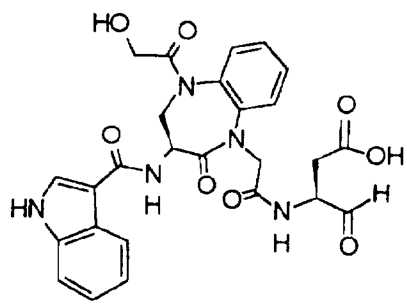

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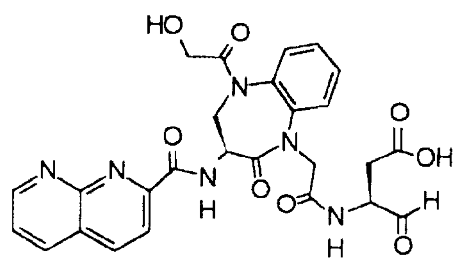

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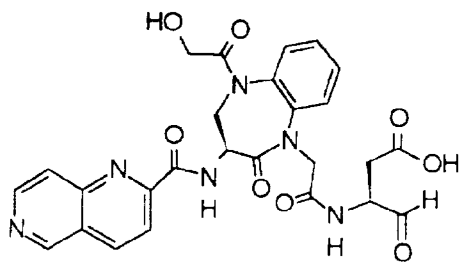

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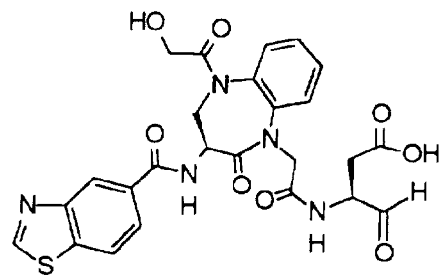
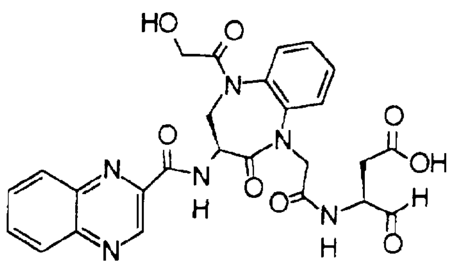
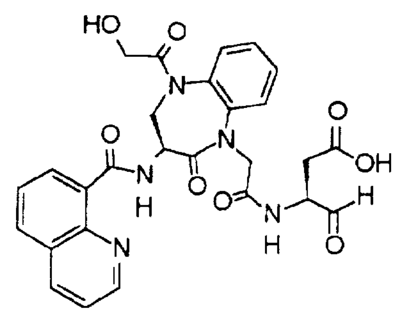
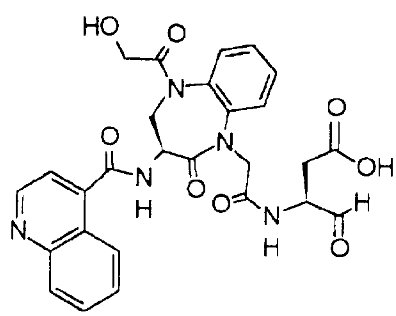
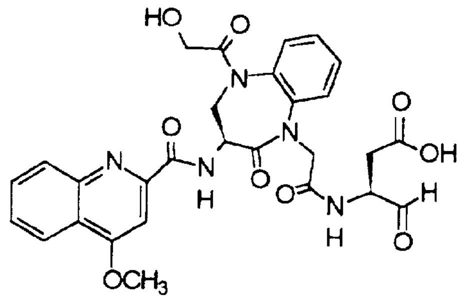
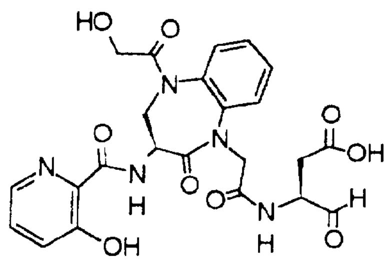
743  ;

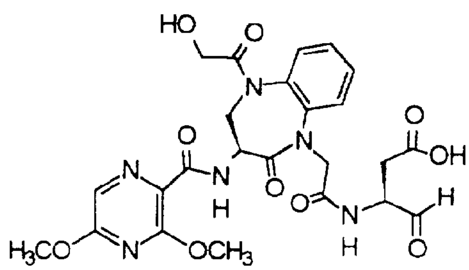
744  ;

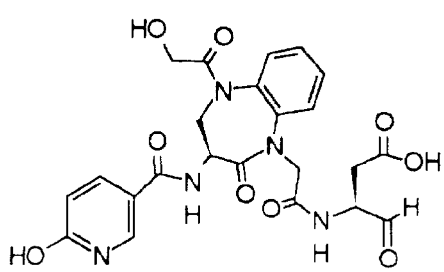
745  ;

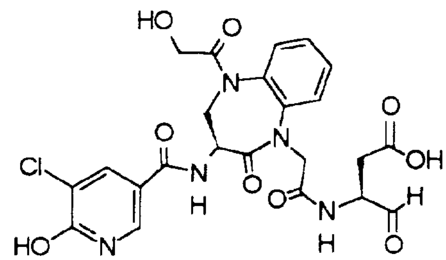
746  ;

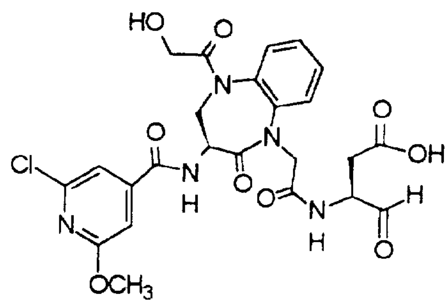
747  ;

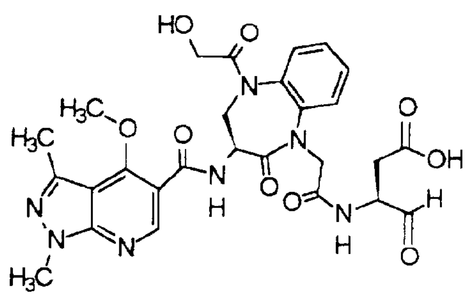
748  ;

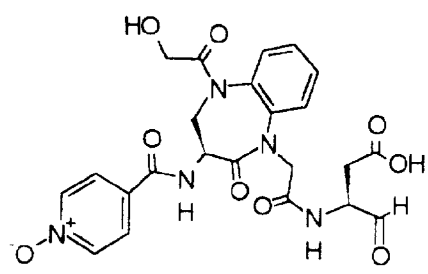
749  ;

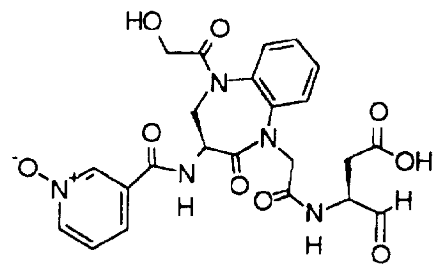
750  ;

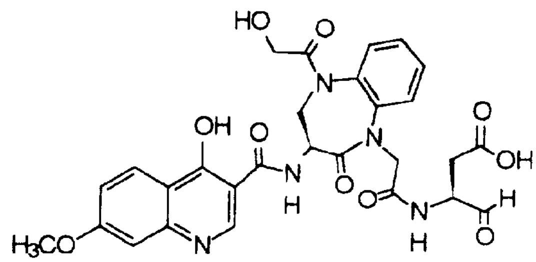
751  ;

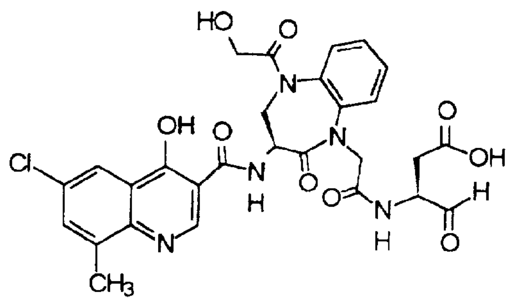
752  ;

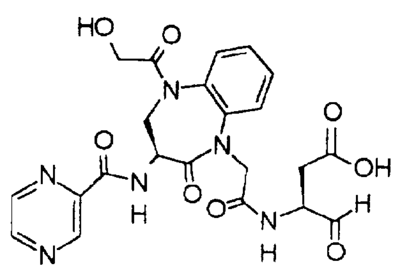
753  ;

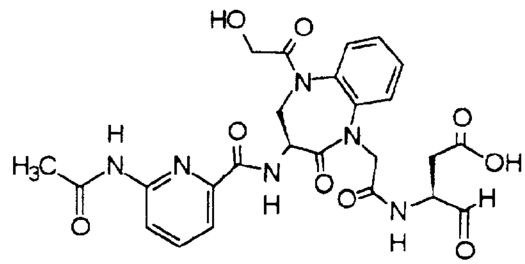
754  ;

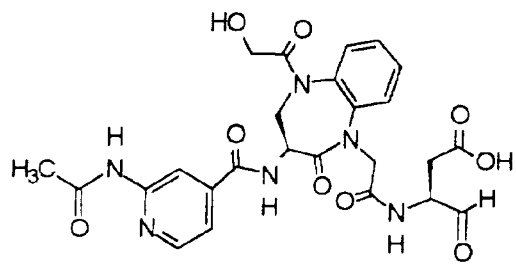
755  ;

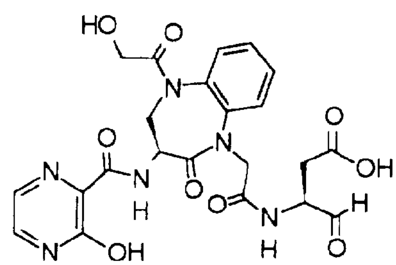
756  ;

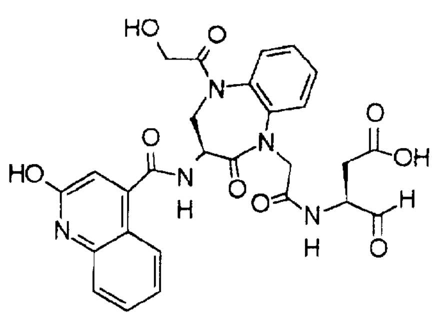
757  ;

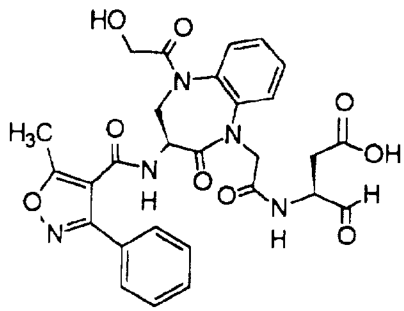
758  ;

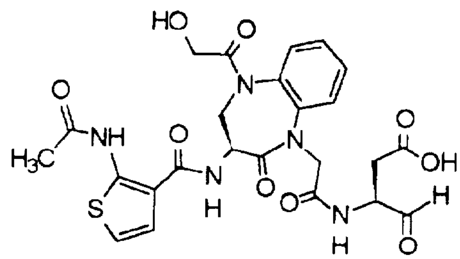
759  ;

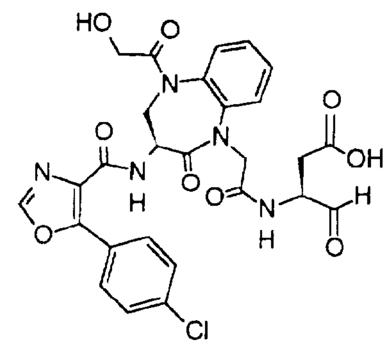
760  ;

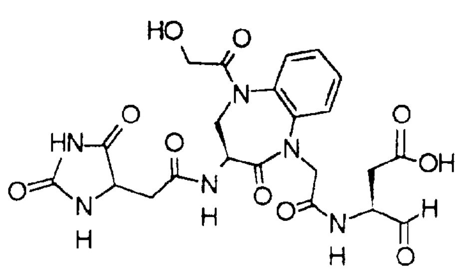
761  ;

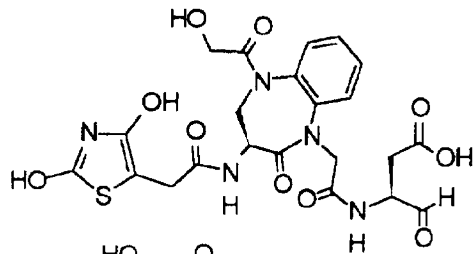
762  ;

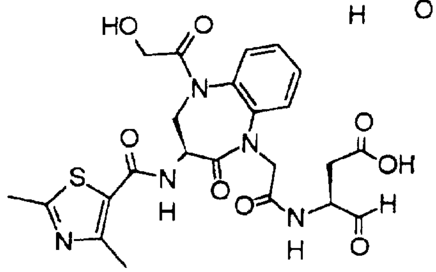
763  ;

764  ;

765  ;

766  ;

767  ; and

801  .

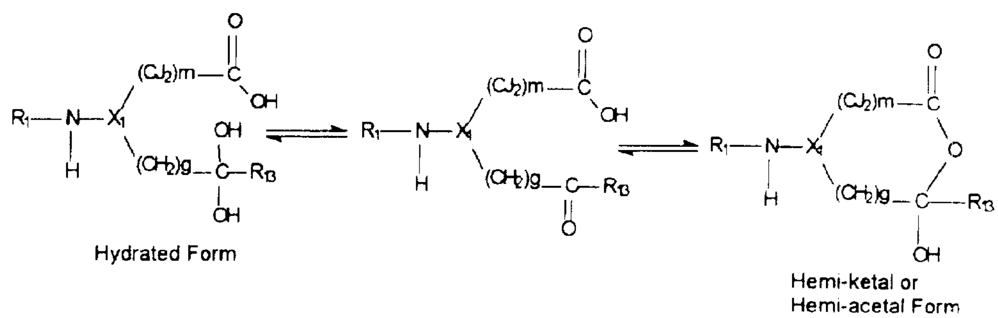
The most preferred compounds of embodiments (K) and (L) are those wherein the Ar_3 cyclic group is isoquinolyl.

Compounds of this invention are described in co-pending United States Application Serial Nos. 08/575,641 and 08/598,332 the disclosures of which are herein incorporated by reference.

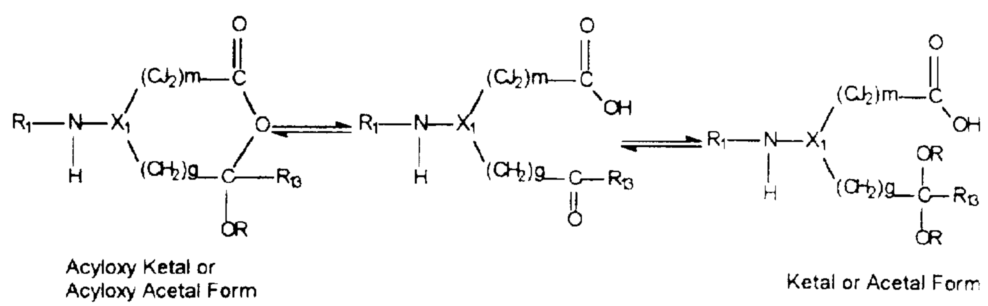
The compounds of this invention have a molecular weight of less than or equal to about 700 Daltons, and more preferably between about 400 and 600 Daltons. These preferred compounds may be readily absorbed by the bloodstream of patients upon oral administration. This oral availability makes such compounds excellent agents for orally-administered treatment and prevention regimens against IL-1-, apoptosis-, IGIF- or IFN-γ mediated diseases.

It should be understood that the compounds of this invention may exist in various equilibrium forms, depending on conditions including choice of solvent, pH, and others known to the practitioner skilled in the art. All such forms of these compounds are expressly included in the present invention. In particular, many

of the compounds of this invention, especially those which contain aldehyde or ketone groups in R_3 and carboxylic acid groups in T, may take hemi-ketal (or hemi-acetal) or hydrated forms. For example, compounds of embodiment (A) may take the forms depicted below: EQ1



Depending on the choice of solvent and other conditions known to the practitioner skilled in the art, compounds of this invention may also take acyloxy ketal, acyloxy acetal, ketal or acetal form:



In addition, it should be understood that the equilibrium forms of the compounds of this invention may include tautomeric forms. All such forms of these compounds are expressly included in the present invention.

It should be understood that the compounds of this invention may be modified by appropriate

functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion. In addition, the compounds may be altered to pro-drug form such that the desired compound is created in the body of the patient as the result of the action of metabolic or other biochemical processes on the pro-drug. Such pro-drug forms typically demonstrate little or no activity in *in vitro* assays. Some examples of pro-drug forms include ketal, acetal, oxime, imine, and hydrazone forms of compounds which contain ketone or aldehyde groups, especially where they occur in the R_3 group of the compounds of this invention. Other examples of pro-drug forms include the hemi-ketal, hemi-acetal, acyloxy ketal, acyloxy acetal, ketal, and acetal forms that are described in EQ1 and EQ2.

ICE and TX Cleave and Thereby Activate Pro-IGIF

The ICE protease was identified previously by virtue of its ability to process inactive pro-IL-1ß to mature active IL-1ß, a pro-inflammatory molecule, in vitro and in vivo . Here we show that ICE and its close homologue TX (Caspase-4, C. Faucheu et al., EMBO, 14, p. 1914 (1995)) can proteolytically cleave inactive pro-IGIF. This processing step is required to convert pro-IGIF to its active mature form, IGIF. Cleavage of pro-IGIF by ICE, and presumably by TX, also facilitates the export of IGIF out of cells.

We first used transient co-expression of plasmids transfected into Cos cells to determine whether any known members of the ICE/CED-3 protease family can process pro-IGIF to IGIF in cultured cells (**Example 23**) (**Fig. 1A**).

Fig. 1A demonstrates that ICE cleaves pro-IGIF in Cos cells co-transfected with plasmids that express pro-IGIF in the presence of active ICE. Cos cells were transfected with an expression plasmid for pro-IGIF alone (lane 2) or in combination with the indicated expression plasmids encoding wild type or inactive mutants of ICE/CED-3 family of proteases (lanes 3-12). Cell lysates were prepared and analyzed for the presence of IGIF protein by immunoblotting with an anti-IGIF antiserum. Lane 1 contained lysates from mock transfected cells.

Co-expression of pro-IGIF with ICE or TX resulted in the cleavage of pro-IGIF into a polypeptide similar in size to the naturally-occurring 18-kDa mature IGIF. This processing event is blocked by single point mutations that alter the catalytic cysteine residues and thus inactivate ICE and TX (Y. Gu et al., EMBO, 14, p. 1923 (1995)).

Co-expression with CPP32 (Caspase-3), a protease involved in programmed cell death (T. Fernandes-Alnemri et al., J. Biol. Chem., 269, p. 30761 (1994); D. W. Nicholson et al., Nature, 376, p. 37 (1995)), resulted in the cleavage of pro-IGIF into a smaller polypeptide, while co-expression with CMH-1 (Caspase-7), a close homolog of CPP32 (J. A. Lippke et al., J. Biol. Chem., 271, p. 1825 (1996)), failed to cleave pro-IGIF to any significant extent. Thus, ICE and TX appear to be capable of cleaving pro-IGIF into a

polypeptide similar in size to the naturally-occurring 18-kDa IGIF.

We next examined the ability of these cysteine proteases to cleave pro-IGIF in vitro using a purified, recombinant $(His)_6$-tagged pro-IGIF as a substrate (**Example 23**).

Fig. 1B demonstrates that pro-IGIF is cleaved in vitro by ICE. Purified recombinant $(His)_6$-tagged pro-IGIF (2 μg) was incubated with the indicated cysteine protease in the presence or absence of ICE or CPP32 inhibitors as described in **Example 23.** The cleavage products were analyzed by SDS-PAGE and Coomassie Blue staining.

ICE cleaved the 24 kDa pro-IGIF into two polypeptides of approximately 18-kDa and 6-kDa. N-terminal amino acid sequencing of the ICE cleavage products indicated that the 18-kDa polypeptide contains the same N-terminal amino acid residues (Asn-Phe-Gly-Arg-Leu) as the naturally occurring IGIF. This shows that ICE cleaves pro-IGIF at the authentic processing site (Asp35-Asn36) (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995)). N-terminal amino acid sequencing of the CPP32 cleavage products indicated that CPP32 cleaved pro-IGIF at Asp69-Ile70.

The cleavage by ICE of pro-IGIF is highly specific with a catalytic efficiency (k_{cat}/K_M) of 1.4 x 10^7 M^{-1} s^{-1} (K_M = 0.6 ± 0.1 μM; k_{cat} = 8.6 ± 0.3 s^{-1}) and is inhibited by specific ICE inhibitors (Ac-Tyr-Val-Ala-Asp-aldehyde) and Cbz-Val-Ala-Asp-[(2,6-dichlorobenzoyl)oxy]methylketone, (N.A. Thornberry et al., Nature, 356, p. 768 (1992); R. E. Dolle et al., J. Med. Chem., 37, p. 563 (1994)).

Fig. 1C demonstrates that ICE cleavage _in vitro_ activates pro-IGIF. Uncleaved pro-IGIF, ICE- or CPP32-cleaved products of pro-IGIF, or recombinant mature IGIF (rIGIF) were each added to A.E7 cell cultures to a final concentration of 12 ng/ml or 120 ng/ml (see, **Example 23**). Eighteen hours later, IFN-γ in the cultural medium was quantified by ELISA. While the uncleaved pro-IGIF had no detectable IFN-γ inducing activity, ICE-cleaved pro-IGIF was active in inducing IFN-γ production in Th1 cells.

Like ICE, the ICE homolog TX also cleaved pro-IGIF into similarly sized polypeptides. However, its catalytic efficiency was about two orders of magnitude lower than that shown for ICE.

Consistent with the observations from the Cos cell experiments above, CPP32 cleaved pro-IGIF at a different site (Asp69-Ile70) and the resulting polypeptides had little IFN-γ inducing activity (**Fig. 1C**). CMH-1 and granzyme B each failed to cleave pro-IGIF to any significant extent.

Together, these results demonstrate that, both in Cos cells and _in vitro_, ICE and TX are capable of processing the inactive pro-IGIF precursor at the authentic maturation site to generate a biologically active IGIF molecule.

Processing of Pro-IGIF by ICE Facilitates Its Export

IGIF is produced by activated Kupffer cells and macrophages _in vivo_ and is exported out of the cells upon stimulation by endotoxin (H. Okamura et al., _Infection and Immunity_, 63, p. 3966 (1995); H. Okamura et al., _Nature_, 378, p. 88 (1995). We used the Cos cell co-expression system (**Example 23**) to examine

whether the intracellular cleavage of pro-IGIF by ICE would facilitate the export of mature IGIF from the cell. Such is the case for pro-IL-1β when it is cleaved by ICE into active IL-1ß (N.A. Thornberry et al., Nature, 356, p. 768 (1992)).

In **Fig. 2A**, Cos cells transfected with an expression plasmid for pro-IGIF alone (lanes 2 and 6) or in combination with an expression plasmid encoding wild type (lanes 3 and 7) or inactive mutant ICE (lanes 4 and 8) were metabolically labeled with ^{35}S-methionine (see, **Example 24**). Cell lysates (left) and conditioned medium (right) were immunoprecipitated with an anti-IGIF antiserum. The immunoprecipitated proteins were analyzed by SDS-PAGE and fluorography (**Fig. 2A**).

An 18-kDa polypeptide corresponding in size to mature IGIF was detected in the conditioned medium of Cos cells co-expressing pro-IGIF and ICE, while Cos cells co-expressing pro-IGIF and an inactive ICE mutant (ICE-C285S), or pro-IGIF alone (-) exported only very low levels of pro-IGIF and no detectable mature IGIF. We estimate that about 10% of the mature IGIF was exported from co-transfected cells, while greater than 99% of pro-IGIF was retained within the cells.

We also measured the presence of IFN-γ inducing activity in cell lysates and in the conditioned medium of the above transfected cells (see, **Example 24**). IFN-γ inducing activity was detected in both cell lysates and the conditioned medium of Cos cells co-expressing pro-IGIF and ICE, but not in cells expressing either pro-IGIF or ICE alone (**Fig. 2B**).

These results indicate that ICE cleavage of pro-IGIF facilitates the export of mature, active IGIF from cells.

<u>Pro-IGIF is a Physiological Substrate of ICE In Vivo</u>

To study the role of ICE in the proteolytic activation and export of IGIF under physiological conditions, we examined the processing of pro-IGIF and export of mature IGIF from lipopolysaccharide (LPS)-activated Kupffer cells harvested from <u>Propiobacterium acnes</u>-elicited wild type and ICE deficient (ICE-/-) mice (**Example 25**).

As shown in **Fig. 3A**, Kupffer cells from ICE-/- mice are defective in the export of IGIF. Kupffer cell lysates of wild type and ICE-/- mice contained similar amounts of IGIF as determined by ELISA. IGIF, however, could be detected only in the conditioned medium of wild type but not of the ICE-/- cells. Thus, ICE-deficient (ICE-/-) mice synthesize pro-IGIF, but fail to export it as extracellular pro-or mature IGIF.

To determine whether ICE-deficient (ICE-/-) mice process intracellular pro-IGIF but fail to export IGIF, Kupffer cells from wild type and ICE-/- mice were metabolically labeled with ^{35}S-methionine and IGIF immunoprecipitation experiments were performed on cell lysates and conditioned media as described in **Example 25**. These experiments demonstrated that unprocessed pro-IGIF was present in both wild type and ICE-/- Kupffer cells. However, the 18-kDa mature IGIF was present only in the conditioned medium of wild type and not ICE-/- Kupffer cells (**Fig. 3B**). This shows that active ICE is required in cells for the export of processed IGIF out of the cell.

In addition, conditioned medium from wild type but not from ICE-/- Kupffer cells contained IFN-γ inducing activity that was not attributed to the action

of IL-12 because it was insensitive to a neutralizing anti-IL-12 antibody. The absence of IGIF in the conditioned medium of ICE-/- Kupffer cells is consistent with the finding in Cos cells that the processing of pro-IGIF by ICE is required for the export of active IGIF.

Figs. 3C and **3D** show that, in vivo, ICE-/- mice have reduced serum levels of IGIF and IFN-γ, respectively. Wild type (ICE+/+) and ICE-/- mice (n=3) primed with heat-inactivated *P. acnes* were challenged with LPS (**Example 26**), and the levels of IGIF (**Fig. 3C**) and IFN-γ (**Fig. 3D**) in the sera of challenged mice were measured by ELISA three hours after LPS challenge (**Example 25**).

The sera of ICE-/- mice stimulated by *P. acnes* and LPS contained reduced levels of IGIF (**Fig. 3C**) and no detectable IFN-γ inducing activity in the presence of an anti-IL-12 antibody. The reduced serum levels of IGIF likely accounts for the significantly lower levels of IFN-γ in the sera of ICE-/- mice (**Fig. 3D**), because we have observed no significant difference in the production of IL-12 in ICE-/- mice under these conditions. Consistent with this interpretation is the finding that non-adherent splenocytes from wild type and ICE-/- mice produced similar amounts of IFN-γ when stimulated with recombinant active IGIF in vitro. Thus the impaired production of IFN-γ is not due to any apparent defect in the T cells of the ICE-/- mice.

Taken together, these results establish a critical role for ICE in processing the IGIF precursor and in the export of active IGIF both in vitro and in

vivo.

To examine in more detail the relationship between serum levels of IFN-γ and ICE activity *in vivo*, a time course after challenge of wild type and ICE-deficient mice with LPS was performed (**Example 26**) (**Fig. 4**).

Fig. 4 shows a time course increase of serum IFN-γ in wild type mice, with sustained levels of ≥17 ng/ml occurring from 9-18 hrs after LPS challenge. As predicted by the experiments discussed above, serum IFN-γ levels were significantly lower in ICE-/- mice, with a maximum of 2 ng/ml achieved over the same time period, which is approximately 15% of the level observed in wild type mice (**Fig. 4**).

Animals were also observed for clinical signs of sepsis and body temperature was measured at 4-hour intervals in wild type and ICE-/- mice challenged with 30 mg/kg or 100 mg/kg LPS (ICE-/-only). Results in **Fig. 4** show that wild type mice experienced a significant decrease in body temperature (from 36°C to 26°C) within 12 hours of LPS challenge. Signs of clinical sepsis were evident and all animals expired within 24-28 hours.

In contrast, ICE-/- mice challenged with 30 mg/kg LPS experienced only a 3°-4°C decrease in body temperature with minimal signs of distress and with no observed lethality. ICE-/- mice challenged with 100 mg/kg LPS experienced clinical symptoms, a decrease in body temperature, and mortality similar to wild type mice at the 30 mg/kg LPS dose.

The ICE Inhibitor Ac-YVAD-CHO is an Equipotent Inhibitor of IL-1ß and IFN-γ Production

Since the processing and secretion of biologically active IGIF is mediated by ICE, we compared the activity of a reversible ICE inhibitor (Ac-YVAD-CHO) on IL-1β and IFN-γ production in a peripheral blood mononuclear cell (PBMC) assay (**Examples 27**).

Results in **Fig. 5** show a similar potency for the ability of the Ac-YVAD-CHO ICE inhibitor to decrease IL-1β and IFN-γ production in human PBMCs, with an IC_{50} of 2.5 μM for each. Similar results were obtained in studies with wild type mouse splenocytes.

These findings provide additional evidence that pro-IGIF is a physiological substrate for ICE and suggest that ICE inhibitors will be useful tools for controlling physiological levels of IGIF and IFN-γ.

In summary, we have found that ICE controls IGIF and IFN-γ levels in vivo and in vitro and that ICE inhibitors can decrease levels of IGIF and IFN-γ in human cells. These results have been described in co-pending United States Application Serial No. 08/712,878, the disclosure of which is herein incorporated by reference.

Compositions and Methods

The pharmaceutical compositions and methods of this invention will be useful for controlling IL-1, IGIF and IFN-γ levels in vivo. The methods and compositions of this invention will thus be useful for treating or reducing the advancement, severity of effects of IL-1, IGIF- and IFN-γ-mediated conditions.

The compounds of this invention are effective ligands for ICE. Accordingly, these compounds are capable of targeting and inhibiting events in IL-1-, apoptosis-, IGIF-, and IFN-γ-mediated diseases, and, thus, the ultimate activity of that protein in inflammatory diseases, autoimmune diseases, destructive bone, proliferative disorders, infectious diseases, and degenerative diseases. For example, the compounds of this invention inhibit the conversion of precursor IL-1β to mature IL-1β by inhibiting ICE. Because ICE is essential for the production of mature IL-1, inhibition of that enzyme effectively blocks initiation of IL-1-mediated physiological effects and symptoms, such as inflammation, by inhibiting the production of mature IL-1. Thus, by inhibiting IL-1β precursor activity, the compounds of this invention effectively function as IL-1 inhibitors.

Similarly, compounds of this invention inhibit the conversion of precursor IGIF to mature IGIF. Thus, by inhibiting IGIF production, the compounds of this invention effectively function as inhibitors of IFN-γ production.

Accordingly, one embodiment of this invention provides a method for decreasing IGIF production in a subject comprising the step of administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an ICE inhibitor and a pharmaceutically acceptable carrier.

Another embodiment of this invention provides a method for decreasing IFN-γ production in a subject comprising the step of administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an ICE inhibitor and a

pharmaceutically acceptable carrier.

In another embodiment, the methods of this invention comprise the step of administering to a subject a pharmaceutical composition comprising an inhibitor of an ICE-related protease that is capable of cleaving pro-IGIF to active IGIF, and a pharmaceutically acceptable carrier. One such ICE-related protease is TX, as described above. This invention thus provides methods and pharmaceutical compositions for controlling IGIF and IFN-γ levels by administering a TX inhibitor.

Other ICE-related proteases capable of processing pro-IGIF into an active IGIF form may also be found. Thus it is envisioned that inhibitors of those enzymes may be identified by those of skill in the art and will also fall within the scope of this invention.

The compounds of this invention may be employed in a conventional manner for the treatment of diseases which are mediated by IL-1, apoptosis, IGIF or IFN-γ. Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a patient suffering from an IL-1-, apoptosis-, IGIF- or IFN-γ-mediated disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that disease.

Alternatively, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against IL-1-, apoptosis-, IGIF- or IFN-γ-mediated diseases over

extended periods of time. The compounds may be employed in such compositions either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of ICE inhibitors in pharmaceutical compositions. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period of time against IL-1-, apoptosis-, IGIF- or IFN-γ- mediated diseases.

The compounds of this invention may also be co-administered with other ICE inhibitors to increase the effect of therapy or prophylaxis against various IL-1-, apoptosis, IGIF- or IFN-γ-mediated diseases.

In addition, the compounds of this invention may be used in combination either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipoxygenase inhibitors and antagonists of cytokines other than IL-1β.

The compounds of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO) or with prostaglandins, to prevent or combat IL-1-mediated disease symptoms such as inflammation.

When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according

to this invention comprise a combination of an ICE inhibitor of this invention and another therapeutic or prophylactic agent.

Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as dα-tocopherol polyethyleneglycol 1000 succinate, or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β- and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2-and 3-hydroxypropyl-β-cyclodextrines, or other solubiliezed derivatives may also be advantageeously used to enhanve delivery of compounds of this invention.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by

inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compounds or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable

oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical

composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-administered transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 1 and 50 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of IL-1-, apoptosis, IGIF and IFN-γ-mediated

diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, necrotic diseases, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, adult respiratory distress syndrome, glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs. host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

Upon improvement of a patient's condition, a

maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence or disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, and the patient's disposition to the disease and the judgment of the treating physician.

The IL-1 mediated diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, and degenerative diseases. The apoptosis-mediated diseases which may be treated or prevented by the compounds of this invention include degenerative diseases.

Inflammatory diseases which may be treated or prevented include, but are not limited to osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, and adult respiratory distress syndrome. Preferably the inflammatory disease is osteoarthritis or acute pancreatitis.

Autoimmune diseases which may be treated or prevented include, but are not limited to, glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, Crohn's disease, psoriasis, and graft vs. host disease. Preferably the autoimmune disease is rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or psoriasis.

Destructive bone disorders which may be treated or prevented include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder.

Proliferative diseases which may be treated or prevented include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Infectious diseases which may be treated or prevented include, but are not limited to, sepsis, septic shock, and Shigellosis.

The IL-1-mediated degenerative or necrotic diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, and myocardial ischemia. Preferably, the degenerative disease is Alzheimer's disease.

The apoptosis-mediated degenerative diseases which may be treated or prevented by the compounds of

this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

The methods of this invention may be used for treating, or reducing the advancement, severity or effects of an IGIF-or IFN-γ-mediated inflammatory, autoimmune, infectious, proliferative, destructive bone, necrotic, and degenerative conditions, including diseases, disorders or effects, wherein the conditions are characterized by increased levels of IGIF or IFN-γ production.

Examples of such inflammatory conditions include, but are not limited to, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative collitis, cerebral ischemia, myocardial ischemia and adult respiratory distress syndrome.

Preferably, the inflammatory condition is rheumatoid arthritis, ulcerative collitis, Crohn's disease, hepatitis and adult respiratory distress syndrome.

Examples of such infectious conditions include, but are not limited to, infectious hepatitis, sepsis, septic shock and Shigellosis.

Examples of such autoimmune conditions include, but are not limited to, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune

neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, acute dermatomyositis, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome.

Preferably the autoimmune condition is glomerulonephritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, psoriasis, graft vs. host disease, including transplant rejection, and hepatitis.

Examples of such destructive bone disorders include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder.

Examples of such proliferative conditions include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Examples of such neurodegenerative conditions include, but are not limited to, Alzheimer's disease, Parkinson's disease and Huntington's disease.

Although this invention focuses on the use of the compounds disclosed herein for preventing and treating IL-1, apoptosis, IGIF- and IFN-γ-mediated diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

The compounds of this invention are also useful as commercial reagents which effectively bind to ICE or other cysteine proteases. As commercial reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide in biochemical or cellular assays for ICE and ICE homologs or may be derivatized to bind to a

stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial cystine protease inhibitors will be evident to those of ordinary skill in the art.

Process of Preparing N-Acylamino Compounds

The ICE inhibitors of this invention may be synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

The compounds of this invention are among the most readily synthesized ICE inhibitors known. Previously described ICE inhibitors often contain four or more chiral centers and numerous peptide linkages. The relative ease with which the compounds of this invention can be synthesized represents an advantage in the large scale production of these compounds.

For example, compounds of this invention may be prepared using the processes described herein. As can be appreciated by the skilled practitioner, these processes are not the only means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described herein may be performed in an alternate sequence or order to give the desired compounds.

This invention also provides a preferred method for preparing the compounds of this invention. Accordingly, in another embodiment (M) is provided a process for preparing an N-acylamino compound comprising the steps of:

a) mixing a carboxylic acid with an N-

alloc-protected amino in the presence of an inert solvent, triphenylphoshine, a nucleophilic scavenger, and tetrakis-triphenyl phosphine palladium(0) at ambient temperature under an inert atmosphere; and

b) adding to the step a) mixture, HOBT and EDC; and optionally comprising the further step of:

c) hydrolyzing the step b) mixture in the presence of a solution comprising an acid and H2O, wherein the step b) mixture is optionally concentrated, prior to hydrolyzing.

Preferably, the inert solvent is CH_2Cl_2, DMF, or a mixture of CH_2Cl_2 and DMF.

Preferably, the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine, or dimethyl barbituric acid. More preferably, the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

Preferably, the solution comprises trifluoroacetic acid in about 1-90% by weight. More preferably, the solution comprises trifluoroacetic acid in about 20-50% by weight.

Alternatively, the solution comprises hydrochloric acid in about 0.1-30% by weight. More preferably, the solution comprises hydrochloric acid in about 0.1-30% by weight.

More preferably, in the above process, the inert solvent is CH_2Cl_2, DMF, or a mixture of CH_2Cl_2 and DMF and the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine, or dimethyl barbituric acid.

Most preferably, in the above process the inert solvent is CH_2Cl_2, DMF, or a mixture of CH_2Cl_2 and DMF and the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

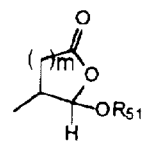
Preferably, the N-acyclamino compound is represented by formula (VIII):

$$\begin{array}{c} R_1-\underset{\displaystyle \overset{|}{H}}{N}-R_2 \end{array}$$

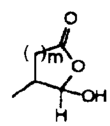
wherein:

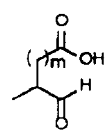
R1 is as defined above in embodiment (A);

R2 is:

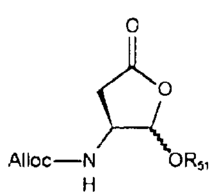
(a)  ,

wherein R_{51} is as defined above in embodiment (B);

(b)  , or

(c)  ;

Preferably, the N-alloc-protected amine is:



, wherein R_{51} is as defined above.

In preferred processes, the substituents are as defined in embodiment (A).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined

above in embodiment (B) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (B).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (C) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (C).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (D) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (D).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (E) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (E).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (F) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (F).

Alternatively, the N-acylamino compound is

represented by formula (VIII), wherein R_1 is as defined above in embodiment (G) and R_2 is as defined above in embodiment (G).

Preferably in these alternative processes, the substituents are as defined above in embodiment (G).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (H) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (H).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (I) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (I).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (J) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (J).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (K) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (K).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (L) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (L).

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

Example 1

Inhibition of ICE

We obtained inhibition constants (K_i) and IC_{50} values for compounds of this invention using the three methods described below:

1. Enzyme assay with UV-visible substrate

This assay is run using an Succinyl-Tyr-Val-Ala-Asp-pNitroanilide substrate. Synthesis of analogous substrates is described by L. A. Reiter (Int. J. Peptide Protein Res. 43, 87-96 (1994)). The assay mixture contains:

65 µl buffer (10mM Tris, 1 mM DTT, 0.1% CHAPS @pH 8.1)
10 µl ICE (50 nM final concentration to give a rate of ~1mOD/min)
5 µl DMSO/Inhibitor mixture
20 µl 400µM Substrate (80 µM final concentration)
100µl total reaction volume

The visible ICE assay is run in a 96-well microtiter plate. Buffer, ICE and DMSO (if inhibitor is present) are added to the wells in the order listed. The components are left to incubate at room temperature for 15 minutes starting at the time that all components are present in all wells. The microtiter plate reader is set to incubate at 37 °C. After the 15 minute incubation, substrate is added directly to the wells and the reaction is monitored by following the release of the chromophore (pNA) at 405 - 603 nm at 37 °C for 20 minutes. A linear fit of the data is performed and the rate is calculated in mOD/min. DMSO is only present during experiments involving inhibitors, buffer is used to make up the volume to 100 µl in the other experiments.

2. Enzyme Assay with Fluorescent Substrate

This assay is run essentially according to Thornberry et al. (Nature 356: 768-774 (1992)), using substrate 17 referenced in that article. The substrate is: Acetyl-Tyr-Val-Ala-Asp-amino-4-methylcoumarin (AMC). The following components are mixed:

65 µl buffer(10mM Tris,1mM DTT, 0.1% CHAPS @pH8.1)
10 µl ICE (2 - 10 nM final concentration)
5 µl DMSO/inhibitor solution
20 µl 150 µM Substrate (30 µM final)
100µl total reaction volume

The assay is run in a 96 well microtiter plate. Buffer and ICE are added to the wells. The components are left to incubate at 37 °C for 15 minutes in a temperature-controlled wellplate. After the 15 minute incubation, the reaction is started by adding substrate directly to the wells and the reaction is monitored @37 °C for 30 minutes by following the release of the AMC fluorophore using an excitation wavelength for 380 nm and an emission wavelength of 460 nm. A linear fit of the data for each well is performed and a rate is determined in fluorescence units per second.

For determination of enzyme inhibition constants (K_i) or the mode of inhibition (competitive, uncompetitive or noncompetitive), the rate data determined in the enzyme assays at varying inhibitor concentrations are computer-fit to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The determination of second order rate constants for irreversible inhibitors was performed by fitting the fluorescence vs time data to the progress equations of Morrison. Morrison, J.F., Mol. Cell.

Biophys., 2, pp. 347-368 (1985). Thornberry et al. have published a description of these methods for measurement of rate constants of irreversible inhibitors of ICE. Thornberry, N.A., et al. Biochemistry, 33, pp. 3923-3940 (1994). For compounds where no prior complex formation can be observed kinetically, the second order rate constants (k_{inact}) are derived directly from the slope of the linear plots of k_{obs} vs. [I]. For compounds where prior complex formation to the enzyme can be detected, the hyperbolic plots of k_{obs} vs. [I] are fit to the equation for saturation kinetics to first generate K_i and k'. The second order rate constant k_{inact} is then given by k'/K_i.

3. PBMC Cell assay

IL-1β Assay with a Mixed Population of Human Peripheral Blood Mononuclear Cells (PBMC) or Enriched Adherent Mononuclear Cells

Processing of pre-IL-1β by ICE can be measured in cell culture using a variety of cell sources. Human PBMC obtained from healthy donors provides a mixed population of lymphocyte subtypes and mononuclear cells that produce a spectrum of interleukins and cytokines in response to many classes of physiological stimulators. Adherent mononuclear cells from PBMC provides an enriched source of normal monocytes for selective studies of cytokine production by activated cells.

Experimental Procedure:

An initial dilution series of test compound in DMSO or ethanol is prepared, with a subsequent dilution into RPMI-10% FBS media (containing 2 mM L-glutamine, 10 mM HEPES, 50 U and 50 ug/ml pen/strep)

respectively to yield drugs at 4x the final test concentration containing 0.4% DMSO or 0.4% ethanol. The final concentration of DMSO is 0.1% for all drug dilutions. A concentration titration which brackets the apparent K_i for a test compound determined in an ICE inhibition assay is generally used for the primary compound screen.

Generally 5-6 compound dilutions are tested and the cellular component of the assay is performed in duplicate, with duplicate ELISA determinations on each cell culture supernatant.

PBMC Isolation and IL-1 Assay:

Buffy coat cells isolated from one pint human blood (yielding 40-45 ml final volume plasma plus cells) are diluted with media to 80 ml and LeukoPREP separation tubes (Becton Dickinson) are each overlaid with 10 ml of cell suspension. After 15 min centrifugation at 1500-1800 xg, the plasma/media layer is aspirated and then the mononuclear cell layer is collected with a Pasteur pipette and transferred to a 15 ml conical centrifuge tube (Corning). Media is added to bring the volume to 15 ml, gently mix the cells by inversion and centrifuge at 300 xg for 15 min. Resuspend the PBMC pellet in a small volume of media, count cells and adjust to 6 x 10^6 cells/ml.

For the cellular assay, 1.0 ml of the cell suspension is added to each well of a 24-well flat bottom tissue culture plate (Corning), 0.5 ml test compound dilution and 0.5 ml LPS solution (Sigma #L-3012; 20 ng/ml solution prepared in complete RPMI media; final LPS concentration 5 ng/ml). The 0.5 ml additions of test compound and LPS are usually sufficient to mix the contents of the wells. Three control mixtures are run per experiment, with either

LPS alone, solvent vehicle control, and/or additional media to adjust the final culture volume to 2.0 ml. The cell cultures are incubated for 16-18 hr at 37 °C in the presence of 5% CO_2.

At the end of the incubation period, cells are harvested and transferred to 15 ml conical centrifuge tubes. After centrifugation for 10 min at 200 xg, supernatants are harvested and transferred to 1.5 ml Eppendorf tubes. It may be noted that the cell pellet may be utilized for a biochemical evaluation of pre-IL-1β and/or mature IL-1β content in cytosol extracts by western blotting or ELISA with pre-IL-1β specific antisera.

Isolation of Adherent Mononuclear cells:

PBMC are isolated and prepared as described above. Media (1.0 ml) is first added to wells followed by 0.5 ml of the PBMC suspension. After a one hour incubation, plates are gently shaken and nonadherent cells aspirated from each well. Wells are then gently washed three times with 1.0 ml of media and final resuspended in 1.0 ml media. The enrichment for adherent cells generally yields 2.5-3.0 x 10^5 cells per well. The addition of test compounds, LPS, cell incubation conditions and processing of supernatants proceeds as described above.

ELISA:

We have used Quantikine kits (R&D Systems) for measurement of mature IL-1β. Assays are performed according to the manufacturer's directions. Mature IL-1β levels of about 1-3 ng/ml in both PBMC and adherent mononuclear cell positive controls are observed. ELISA assays are performed on 1:5, 1:10 and 1:20 dilutions of supernatants from LPS-positive

controls to select the optimal dilution for supernatants in the test panel.

The inhibitory potency of the compounds can be represented by an IC_{50} value, which is the concentration of inhibitor at which 50% of mature IL-1β is detected in the supernatant as compared to the positive controls.

The skilled practitioner realizes that values obtained in cell assays, such as those described herein, can depend on multiple factors, such as cell type, cell source, growth conditions and the like.

Example 2

Pharmacokinetic Studies in the Mouse

Peptidyl ICE inhibitors are cleared rapidly with clearance rates greater than 100 μ/min/kg. Compounds with lower clearance rates have improved pharmacokinetic properties relative to peptidyl ICE inhibitors.

We obtained the rate of clearance in the mouse (μ/min/kg) for several compounds of this invention using the method described below:

Sample Preparation and Dosing

Compounds were dissolved in sterile TRIS solution (0.02M or 0.05M) at a concentration of 2.5mg/ml. Where necessary to ensure a complete solution, the sample was first dissolved in a minimum of dimethylacetamide (maximum of 5% of total solution volume) then diluted with the TRIS solution.

The drug solution was administered to CD-1 mice (Charles River Laboratories - 26-31g) via the tail

vein at a dose volume of 10ml/kg giving a drug dose of 25mg/kg.

Mice were dosed in groups of 5 for each timepoint (generally from 2 minutes to 2 hours) then at the appropriate time the animals were anaesthetised with halothane and the blood collected into individual heparinized tubes by jugular severance. The blood samples were cooled to 0 °C then the plasma separated and stored at -20 °C until assayed.

Bioassay

Drug concentration in the plasma samples were determined by HPLC analysis with UV or MS (ESP) detection. Reverse phase chromatography was employed using a variety of bonded phases from C1 to C18 with eluents composed of aqueous buffer/acetonitrile mixtures run under isocratic conditions.

Quantitation was by external standard methods with calibration curves constructed by spiking plasma with drug solutions to give concentrations in the range of 0.5 to 50μg/ml.

Prior to analysis the plasma samples were deproteinated by the addition of acetonitrile, methanol, trichloroacetic acid or perchloric acid followed by centrifugation at 10,000g for 10 minutes. Sample volumes of 20μl to 50μl were injected for analysis.

Compound 214e

Dosing and sampling

The drug was dissolved in sterile 0.02M Tris to give a 2.5mg/ml solution which was administered to 11 groups of 5 male CD-1 mice via the tail vein at a dose of 25mg/kg. At each of the following timepoints: 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes a

group of animals was anaesthetised and the blood collected into heparinized tubes. After separation the plasma was stored at -20 °C until assayed.

Assay

Aliquots of plasma (150µl) were treated with 5% perchloric acid (5µl) then mixed by vortexing and allowed to stand for 90 minutes prior to centrifugation. The resulting supernatant was separated and 20µl was injected for HPLC analysis.

HPLC Conditions

Column	100 x 4.6mm	Kromasil KR 100 5C4
Mobile Phase	0.1m Tris pH7.5	86%
	Acetonitrile	14%
Flowrate	1ml/min	
Detection	UV at 210nm	
Retention Time	3.4 mins	

The results of the analysis indicated a decrease in the mean plasma level of the drug from ~ 70µg/ml at 2 minutes to < 2µg/ml at 90 and 120 minutes.

Compound 217e

Dosing and sampling

The drug was dissolved in sterile 0.02M Tris to give a 2.5mg/ml solution which was administered to 11 groups of 5 male CD-1 mice via the tail vein at a dose of 25mg/kg. At each of the following timepoints: 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes a group of animals was anaesthetised and the blood collected into heparinized tubes. After separation the plasma was stored at -20 °C until assayed.

Assay

Aliquots of plasma (100µl) were diluted with acetonitrile (100µl) then mixed by vortexing for 20 seconds before centrifugation for 10 minutes. The resulting supernatant was separated and 20µl was injected for HPLC analysis.

HPLC Conditions

Column	150 x 4.6mm	Zorbax SBC8
Mobile Phase	0.05M Phosphate buffer ph7.1	72%
	Acetonitrile	28%
Flowrate	1.4ml/min	
Detection	UV at 210nm	
Retention Time	3.0 and 3.6 mins (diasteromers)	

The results of the analysis indicated a decrease in mean plasma concentrations from ~ 55µg/ml at 2 minutes to < 0.2µg/ml at 60-120 minutes.

Example 3

Peptidyl ICE inhibitors are cleared rapidly with clearance rates greater than 80 ml/min/kg. Compounds with lower clearance rates have improved pharmacokinetic properties relative to peptidyl ICE inhibitors.

We obtained the rate of clearance in the rat (ml/min/kg) for several compounds of this invention using the method described below:

In vivo Rat Clearance Assay

Cannulations of the jugular and carotid vessels of rats under anesthesia were performed one day prior to the pharmacokinetic study. M.J. Free, R.A.

Jaffee; 'Cannulation techniques for the collection blood and other bodily fluids'; in: Animal Models; p. 480-495; N.J. Alexander, Ed.; Academic Press; (1978). Drug (10mg/mL) was administered via the jugular vein in a vehicle usually consisting of: propylene glycol/saline, containing 100mM sodium bicarbonate in a 1:1 ratio. Animals were dosed with 10-20 mg drug/kg and blood samples were drawn at 0, 2, 5, 7, 10, 15, 20, 30, 60, and 90 minutes from an indwelling carotid catheter. The blood was centrifuged to plasma and stored at -20 °C until analysis. Pharmacokinetic analysis of data was performed by non-linear regression using standard software such as RStrip (MicroMath Software, UT) and/or Pcnonlin (SCI Software, NC) to obtain clearance values.

Analytical:

Rat plasma was extracted with an equal volume of acetonitrile (containing 0.1% TFA). Samples were then centrifuged at approximately 1,000 x g and the supernatant analyzed by gradient HPLC. A typical assay procedure is described below.

200 µL of plasma was precipitated with 200 µL of 0.1% trifluoroacetic acid (TFA) in acetonitrile and 10 µL of a 50% aqueous zinc chloride solution, vortexed then centrifuged at ~1000 x g and the supernatant collected and analyzed by HPLC.

HPLC procedure:

Column:	Zorbax SB-CN (4.6 x 150 mm) (5µ particle size)
Column temperature:	50 °C
Flow rate:	1.0 mL/min
Injection volume:	75 µL.
Mobile phase:	A=0.1% TFA in water and B=100% acetonitrile

Gradient employed:	100% A to 30% A in 15.5 min
	0% A at 16 min
	100% A at 19.2 min
Wavelength:	214 nm

A standard curve was run at 20, 10, 5, 2 and 1 μg/mL concentrations.

Example 4

Whole Blood Assay for IL-1ß Production

We obtained IC_{50} values for several compounds of this invention using the method described below:

Purpose:

The whole blood assay is a simple method for measuring the production of IL-1b (or other cytokines) and the activity of potential inhibitors. The complexity of this assay system, with its full complement of lymphoid and inflammatory cell types, spectrum of plasma proteins and red blood cells is an ideal in vitro representation of human in vivo physiologic conditions.

Materials:

Pyrogen-free syringes (~ 30 cc)

Pyrogen-free sterile vacuum tubes containing lyophilized Na_2EDTA (4.5 mg/10 ml tube)

Human whole blood sample (~ 30-50 cc)

1.5 ml eppendorf tubes

Test compound stock solutions (~ 25mM in DMSO or other solvent)

Endotoxin-free sodium chloride solution (0.9%) and HBSS

Lipopolysaccharide (Sigma; Cat.# L-3012) stock solution at 1mg/ml in HBSS

IL-1β ELISA Kit (R & D Systems; Cat # DLB50)
TNFα ELISA Kit (R & D Systems; Cat # DTA50)
Water bath or incubator

Whole Blood Assay Experimental Procedure:

Set incubator or water bath at 30 °C. Aliquot 0.25ml of blood into 1.5 ml eppendorf tubes. **Note**: be sure to invert the whole blood sample tubes after every two aliquots. Differences in replicates may result if the cells sediment and are not uniformly suspended. Use of a positive displacement pipette will also minimize differences between replicate aliquots.

Prepare drug dilutions in sterile pyrogen-free saline by serial dilution. A dilution series which brackets the apparent K_i for a test compound determined in an ICE inhibition assay is generally used for the primary compound screen. For extremely hydrophobic compounds, we have prepared compound dilutions in fresh plasma obtained from the same blood donor or in PBS-containing 5% DMSO to enhance solubility.

Add 25 µl test compound dilution or vehicle control and gently mix the sample. Then add 5.0 µl LPS solution (250 ng/ml stocked prepared fresh: 5.0 ng/ml final concentration LPS), and mix again. Incubate the tubes at 30 °C in a water bath for 16-18 hr with occasional mixing. Alternatively, the tubes can be placed in a rotator set at 4 rpm for the same incubation period. This assay should be set up in duplicate or triplicate with the following controls: negative control- no LPS; positive control- no test inhibitor; vehicle control- the highest concentration of DMSO or compound solvent used in the experiment.

Additional saline is added to all control tubes to normalize volumes for both control and experimental whole blood test samples

After the incubation period, whole blood . samples are centrifuged for 10 minutes at ~ 2000 rpm in the microfuge, plasma is transferred to a fresh microfuge tube and centrifuged at 1000 x g to pellet residual platelets if necessary. Plasma samples may be stored frozen at -70 °C prior to assay for cytokine levels by ELISA.

ELISA:

We have used R & D Systems (614 McKinley Place N.E. Minneapolis, MN 55413) Quantikine kits for measurement of IL-1β and TNF-α. The assays are performed according to the manufacturer's directions. We have observed IL-1β levels of ~ 1-5 ng/ml in positive controls among a range of individuals. A 1:200 dilution of plasma for all samples has been sufficient in our experiments for ELISA results to fall on the linear range of the ELISA standard curves. It may be necessary to optimize standard dilutions if you observe differences in the whole blood assay. Nerad, J.L. et al., J. Leukocyte Biol., 52, pp. 687-692 (1992).

Example 5
Inhibition of ICE homologs

1. Isolation of ICE homologs

Expression of TX in insect cells using a baculovirus expression system. We have subcloned Tx cDNA (Faucheu et al., supra 1995) into a modified pVL1393 transfer

vector, co-transfected the resultant plasmid (pVL1393/TX) into insect cells with viral DNA and identified the recombinant baculovirus. After the generation of high titer recombinant virus stock, the medium was examined for TX activity using the visible ICE assay. Typically, infection of Spodoptera frugiperda (Sf9) insect cells at an MOI of 5 with recombinant virus stock resulted in a maximum expression after 48 hours of 4.7μg/ml. ICE was used as a standard in the assay.

Amino terminal T7 tagged versions of ICE or TX were also expressed. Designed originally to assist the identification and purification of the recombinant proteins, the various constructs have also allowed examination of different levels of expression and of the relative levels of apoptosis experienced by the different homologs. Apoptosis in the infected Sf9 cells (examined using a Trypan Blue exclusion assay) was increased in the lines expressing ICE or TX relative to cells infected with the viral DNA alone.

Expression and purification of N-terminally (His)$_6$-tagged CPP32 in *E. coli*. A cDNA encoding a CPP32 (Fernandes-Alnemri et al, <u>supra</u> 1994) polypeptide starting at Ser (29) was PCR amplified with primers that add in frame XhoI sites to both the 5' and 3' ends of the cDNA and the resulting XhoI fragment ligated into a Xho I-cut pET-15b expression vector to create an in frame fusion with (his)$_6$ tag at the n-terminus of the fusion protein. The predicted recombinant protein starts with the amino acid sequence of MGSS<u>HHHHHH</u>SSG<u>LVPRGS</u>HMLE, where LVPRGS represents a thrombin cleavage site, followed by CPP32 starting at

Ser (29). *E. coli* BL21(DE3) carrying the plasmid were grown to log phase at 30 °C and were then induced with 0.8 mM IPTG. Cells were harvested two hours after IPTG addition. Lysates were prepared and soluble proteins were purified by Ni-agarose chromatography. All of the expressed CPP32 protein was in the processed form. N-terminal sequencing analysis indicated that the processing occurred at the authentic site between Asp (175) and Ser (176). Approximately 50 μg of CPP32 protein from 200 ml culture. As determined by active site titration, the purified proteins were fully active. The protease preparation were also very active in vitro in cleaving PARP as well as the synthetic DEVD-AMC substrate (Nicholson et al, supra 1995).

2. Inhibition of ICE homologs

The selectivity of a panel of reversible inhibitors for ICE homologs is depicted in Table 1. ICE enzyme assays were performed according to Wilson et al (supra 1994) using a YVAD-AMC substrate (Thornberry et al, supra 1992). Assay of TX activity was performed using the ICE substrate under identical conditions to ICE. Assay of CPP32 was performed using a DEVD-AMC substrate (Nicholson et al., supra 1995). In general, there is low selectivity between ICE and TX for a wide range of scaffolds. None of the synthetic ICE compounds tested are effective inhibitors of CPP32. Assay of the reversible compounds at the highest concentration (1 μM) revealed no inhibition.

Table 1

Compound	K_i ICE (nM)	K_i TX (nM)	K_i CPP32 (nM)
214e	7.5	7.0 ± 1.1	> 1000
135a	90	55 ± 9	>1000
125b	60	57 ± 13	> 1000
137	40	40 ± 7	> 1000

Second-order rate constants for inactivation of ICE and ICE homologs with selected irreversible inhibitors are presented below (Table 2). The irreversible compounds studied are broad spectrum inhibitors of ICE and its homologs. Some selectivity, however, is observed with the irreversible compounds comparing inhibition of ICE and CPP32.

Table 2

Compound	k_{inact} (ICE) M^{-1} s^{-1}	k_{inact} (TX) M^{-1} s^{-1}	k_{inact} (CPP32) M^{-1} s^{-1}
138	120,000	150,000	550,000
217d	475,000	250,000	150,000
108a	100,000	25,000	nd

Example 6

Inhibition of apoptosis

Fas-Induced Apoptosis in U937 cells. Compounds were evaluated for their ability to block anti-Fas-induced apopotosis. In a preliminary experiment using RT-PCR, we detected mRNA encoding ICE, TX, ICH-1, CPP32 and

CMH-1 in unstimulated U937 cells. We used this cell line for apoptosis studies. U937 cells were seeded in culture at 1 x 10^5 cells/ml and grown to ~5 x 10^6 cells/ml. For apoptosis experiments, 2 x 10^6 cells were plated in 24-well tissue culture plates in 1 ml RPMI-1640-10% FBS and stimulated with 100 ng/ml anti-Fas antigen antibody (Medical and Biological Laboratories, Ltd.). After a 24 hr incubation at 37 °C, the percentage of apoptotic cells was determined by FACS analysis using ApoTag reagents.

All compounds were tested initially at 20 μM and titrations were performed with active compounds to determine IC_{50} values. Inhibition of apoptosis (> 75% at 20 μM) was observed for **108a**, **136**, and **138**. An IC_{50} of 0.8 μM was determined for **217e** compared to no inhibition of anti-Fas-induced apoptosis by **214e** at 20 μM.

Example 7

In vivo acute assay for efficacy as anti-inflammatory agent

LPS-Induced IL-1ß Production.

Efficacy of **214e** and **217e** was evaluated in CD1 mice (n=6 per condition) challenged with LPS (20 mg/kg IP). The test compounds were prepared in olive oil:DMSO:ethanol (90:5:5) and administered by IP injection one hour after LPS. Blood was collected seven hours after LPS challenge. Serum IL-1β levels were measure by ELISA. Results in **Fig. 6** show a dose dependent inhibition of IL-1β secretion by **214e**, with

an ED_{50} of approximately 15 mg/kg. Similar results were obtained in a second experiment. A significant inhibition of IL-1β secretion was also observed in **217e** treated mice (**Fig. 7**). However, a clear dose response was not apparent.

Compounds **214e** and **217e** (50 mg/kg) were also administered by oral gavage to assess absorption. Results in **Fig. 8** show that **214e**, but not **217e** when administered orally inhibited IL-1β secretion, suggesting potential for oral efficacy of ICE inhibitors as anti-inflammatory agents.

The efficacy of analogs of **214e** were also evaluated in LPS challenged mice after IP administration (**Fig. 9**) and PO administration (**Fig. 10**).

__Table 3__ % Inhibition of IL-β production by analogs of **214e** in LPs-chellenged mice after PO and IP administration (50 mg/kg).

__Table 3__

Compound	PO% Inhibition	IP% Inhibition
214e	75	78
265	27	30
416	52	39
434	80	74
438	13	40
442	10	0
2002	-	78

Table 4

Comparison of 214e Prodrugs for Efficacy in LPS Challenged Mice: Time Course Inhibition of IL-1β Production

	Time of Compound Administration (relative to time of LPS challenge, PO, 50 mg/kg			
Compound	-2 hr	-1 hr	0 hr	+1 hr
214e	39* 43* -*	-* 44* -*	80* 48* -*	55% 75* 11* 47*
304a	30	33	68	37
2100e	49	54	94	66
2100a	8	71	67	58
213e	0	48	41	89
302	0	27	21	26
2100c	0	0	85	40
2100d	42	35	52	26
2100b	0	0	47	26
2001	~63 64*	~62 62*	~57 58*	~54 55*

* Values obtained in subsequent assays

Example 8

Measurement of blood levels of prodrugs of 214e.

Mice were administered a p.o. dose of compounds **302** and **304a** (50 mg/kg) prepared in 0.5 % carboxymethylcellulose. Blood samples were collected at 1 and 7 hours after dosing. Serum was extracted by precipitation with an equal volume of acetonitrile containing 2 % formic acid followed by centrifugation. The supernatant was analyzed by liquid chromatography-mass spectrometry (ESI-MS) with a detection level of 0.03 to 3 μg/ml. Compounds **302** and **304a** showed detectable blood levels when administered orally, **214e** itself shows no blood levels above 0.10 μg/mL when administered orally. Compounds **302** and **304a** are prodrugs of **214e** and are metabolized to **214e** in vivo (see **Fig. 11**).

Example 9

We obtained the following data (see Tables 5 and 6) for compounds of this invention using the methods described in Examples 1-8. The structures of the compounds of Example 9 are shown in Example 10-17.

Table 5

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
47b	27	1800	<600	338	
47a	19	2600	5100	79	32
135a	90	2800	5000	>100	

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
135b	320	1600	1700		
125b	60	800	4500		
108b	400	25000			>100
137	40	1700	14000		
139	350	2000			
213e	130	900	600 400*		
214c	1200	5000			
214e	7.5	1600	1300	23	12
217c		1700	7000	70	
217e		175	2000	>50	
220b	600	2125			
223b	99	5000		>100	
223e	1.6	3000	>20000	89	
226e	15	1100	1800	109	
227e	7	234	550		
230e		325	300	67	
232e	1100	4500		22	26
235e	510	4750		36	
238e	500	4250			
246	12	950	10000	31	
257	13	11000 6600*			
265	47	4300	1400	23	20
281	50	600 2500*			
302	4500	>20000	>20000		
304a	200	1,400	2400 14000*		
307a	55	14500	16000		
307b	165		14000		
404	2.9	1650 1800*	1100	64	24
405	6.5	1700	2100		
406	4	1650	2300		
407	0.4	540	1700		
408	0.5	1100	1000	41	23

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
409	3.7	2500			
410	17	2000	2800	32	20
411	0.9	540	1900		
412	1.3	580 660*	700 1000*		25
413	750	6200			
415	2.5	990 1000*	450 3500*	26	18
416	12	1200	3400		47
417	8	2000	6000	33	22
418	2.2	1050 2200*	7800 1800*	13	5.9
419	280	>8000			
420	1200	8000 >8000*			
421	200	4300 4600*			
422	50	2200	1200		
423	10	2100 1800*	1500		45
424	45	2500	4000		
425	0.8	650 700*	650		
426	90	4500 2500*			
427	180	4500			36
428	280				
429	7000				
430	60	>8000			
431	8	>8000	8000		
432	1.6	560	2000		
433	2.9	1000 1100*	1100		
434	4.9	1600 1200*	1800 1300*		20
435	8	4400			
436	7.5	2700			
437	12	1800	5000		

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
438	28	1000	700 2900*		22
439	3.7	2800	3200 3400*		
440	2.3	5000	2000		
441	1	2500	4500		
442	3.2	900	2000		54
443	3.6	2800	1500		
444	15	3500	3500		
445	135		4000		
446	62		3000		
447	5.8	2500	1500		
448	130		4000		
449	12	1500	3200 13000*		
450	5	800	2200 1700*	18	12
451	4	1800	1500 9000*		
452	4.5	600 800*	650 1600*		27.3
453	0.65	1300	1900 1600*		
454	45	2500			
455	1.2	400	2800 2600*		54
456	4.5	600 1300*	600 1400*		12.7
457	6.2	2000	3500		
458	20	2900			
459	5	1800			
460	115	400	2400		
461	47				
462	40				
463	14	2400 2800*			
464	2.5	1000	>1000 2500*		
465	3	1000	800		

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
466	0.8	1400	600		
467	11	1900			
468	4.5	850	2500		
470	5	500	360 500*		63
471	1	750	400		17
472	140				
473	1	1000	400 450*		
474	85				
475	5.5	690 650*	400 350*	31	21
476	7	1600	2500		
477	60				
478	380				
479	15	900	700 2400*		
480	25	2300			
481	1.2	390 930*	600 500*		34
482	<0.2	340	380 260*		
483	1.7	900	700		
484	2	1550 1400*	5000		15
485	2	900	900		
486	2.3	480 570*	500		37
487	2.4	650 950*	500 400*		20
488	1.5	940	750		
489	6	2250 1700*	15000		
490	4.3	980 1000*	700 1900*		
491	5	2500			
493	25	1200	800 850*		

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
494	15	1350 1500*	7000		
495	43				
496	16	1550 1600*	6000		
497	3.5	740	350 700*		
498	1.5	560	500 400*		
499	3.5	1200 800*	9000		
605a	90	2600	>20000		
605b	45	10000		97	
605c	615	4500		37	
605d	95	5100	16000 5100*	33	
605e	29	2250	>10000		24
605f	475	12500			
605g	165	22500			
605h	460	>25000			
605i	680	>20000			
605j	110	8750		71	
605m	650	20000			
605n	12	2100	>20000	28	
605o	72		18000		
605p	125	3200	>20000		
605q	1000				
605s	150	6000			
605t	33				
609a	114	>30000			
609b	27	>20000			
619	300				
620	35	1000	19000		
621	7.2	1300	>20000		
622	35	1300	>20000		
623	9				
624	300				

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
625	105				
626	260				
627	43	3250	8000		
628	36	2750	>20000		
629	230				
630	270				
631	805				
632	148				
633	92	5750	20000		
634	1400				
635	55	1900 3400*	4000		
605v	1100	>30000			
2201	9	2000 3700*	3500		60
2100e	250	800	600		
2100a	100	1100	850		
2002	4	810 860*	70 1400*		32
2100d	>100000	>20000	>20000		
2100c	7400	>20000	>20000		
2100b	8000	>20000	>20000		
2001	135	1800	3500		
1027	4000	>20000	>20000		60
1015	40	2500	1700		23

Table 6

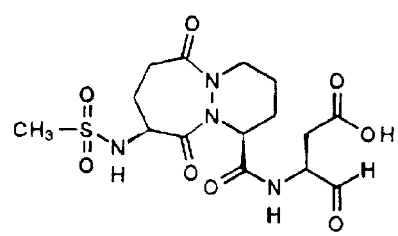
Compound	Fluorescent Assay k_{inact} M^{-1} s^{-1}	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
108a	$1x10^5$	17500			
136	$5.4x10^5$	870	2800	93	

Compound	Fluorescent Assay k_{inact} M^{-1} s^{-1}	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
138	$1.2x10^5$	900	2900	116	
217d	$4.7x10^5$	340	4000		
280	$4x10^5$	650	>1000		187
283	$1x10^5$	<200	450		104
284	$3.5x10^5$	470	550	77	100
285	$4.3x10^5$	810	1000	130	50

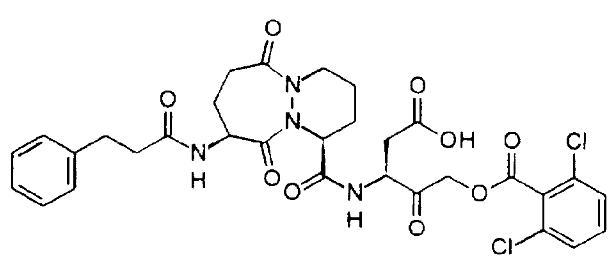
* Values obtained upon reassay.

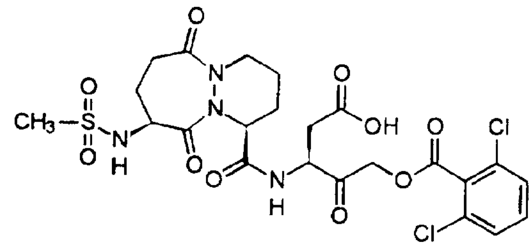
Example 10

Compound **139** was synthesized by a method similar to the method used to synthesize **47a**.

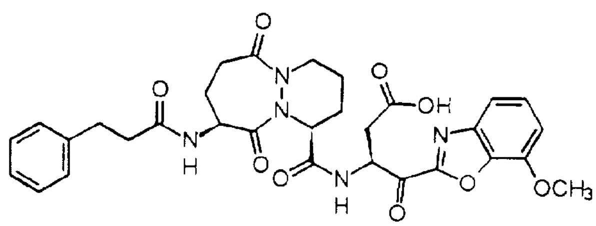
139 

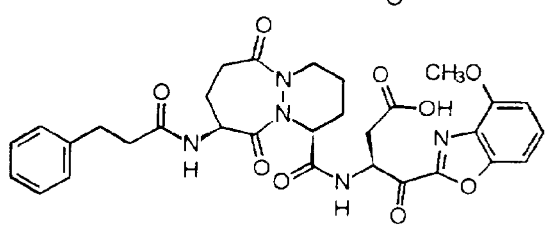
Compounds **136** and **138** were synthesized by a method similar to the method used to synthesize **57b**.

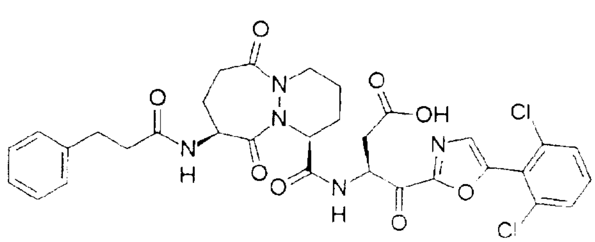
136  ; and

138 .

Compounds **135a**, **135b**, and **137** were synthesized by a method similar to the method used to synthesize **69a**.

135a ;

135b ; and

137 .

Compounds **813e**, **814c**, **814e**, **817c**, **817d**, **817e**, **820b**, **823b**, **823e**, **826e**, **827e**, **830e**, **832e**, **835e**, **838e**, **846**, **857**, **865**, **902**, **904a**, **907a**, **907b**, **1004-1013**, **1015-**

1045, **1046-1068**, **1070-1091**, and **1093-1099** were synthesized by methods similar to those used to synthesize compound **264** and the corresponding compounds in Examples 10 and 11.

Compounds **47a**, **47b**, **108a**, **108b**, **125b**, **213e**, **214c**, **217c**, **217d**, **217e**, **220b**, **223b**, **223e**, **226e**, **227e**, **230e**, **232e**, **235e**, **238e**, **246**, **257**, **264**, **265**, **280-287**, **302**, **304a**, **307a**, and **307b** were synthesized as described below.

H. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-3-amino-4-oxobutanoic acid.

Step A. N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

Reaction of N-tert-butoxycarbonylpipecolic acid (460 mg, 2.0 mmol) and N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (530 mg, 1.82 mmol) was carried out by a method analogous to that reported by Chapman (Bioorg. & Med. Chem. Lett. 2, pp. 613-618, (1992)) to give 654 mg of the title compound.

^{1}H NMR (500 MHz, $CDCl_3$ (existing as rotamers)) δ 7.35 (m, 5H), 6.88 (br. s, 1H), 4.9-4.45(m, 4H), 3.95+ (br. m, 2H), 3.06 (m, 1H), 2.9 (m, 1H), 2.7 (br. m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 1.7-1.5 (m, 3H), 1.45 (two s, 9H).

Step B. N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxo-tetrahydrofuran (654 mg) was dissolved in 15 ml of 25% trifluoroacetic acid in dichloromethane

and stirred at room temperature. The mixture was concentrated to give a gummy residue. The residue was dissolved in dichloromethane and washed with 10% sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give 422 mg of the title compound as a beige solid.

^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 5H), 7.15 (d, 1H), 5.55 (d, 1H), 4.95-4.8 (m, 1H), 4.78 (m, 1H), 4.65 (d, 1H), 4.45 (m, 1H), 3.2 (m, 0.5H), 3.05 (m, 0.5H), 2.95 (m, 0.5H), 2.85 (m, 0.5H), 2.65 (m, 1H), 2.55-2.38(m, 1H), 1.95 (m, 1H), 1.8 (m, 1H), 1.6 (m, 2H), 1.38 (m, 2H).

Step C. <u>N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-oxo-tetrahydrofuran</u>.

N-Acetyl-tyrosinyl-valine (464 mg, 1.44 mmol) and N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (412 mg, 1.3 mmol) were dissolved in 5 ml each of dimethylformamide and dichloromethane and cooled to 0°C. To the cooled solution was added 1-hydroxybenzotriazole (HOBT; 210 mg, 1.56 mmol) followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC; 326 mg, 1.7 mmol). After stirring for 18 hours, the mixture was diluted with ethyl acetate and washed with water, 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and water. The organic layer was concentrated to give a crude solid that was purified by flash chromatography (SiO_2) eluting with 94:6:1

(dichloromethane:isopropanol:pyridine) to give 370 mg of the title compound.

^{1}H NMR (500 MHz, CD_3OD (existing as diastereomers as well as rotamers)) δ 7.35 (m, 5H), 7.05 (m, 2H), 6.68 (m, 2H), 5.65 & 5.25 (m, 1H), 4.9-3.95 (m, 8H), 3.4-2.6 (m, 4H), 2.5-2.1 (m, 1H), 1.98 (s, 1H), 1.9 (s, 1H), 1.85 (s, 1H), 1.8-1.6 (m, 2H), 1.55-1.3 (m, 4H), 0.95-0.85 (m, 6H).

Step D. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-3-amino-4-oxobutanoic acid.

To a solution of 100 mg of N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran in 10 ml of methanol was added 60 mg of $Pd(OH)_2$ on carbon and the mixture placed under an atmosphere of hydrogen via a balloon. The mixture was filtered through Celite and concentrated providing a white solid. This crude solid was dissolved in 2 ml of methanol and triturated with diethyl ether affording 26 mg of the title compound.

^{1}H NMR (500 MHz, CD_3OD(existing as diastereomers as well as rotamers)) δ 7.1 (m, 2H), 6.7 (m, 2H), 5.2 (br. m, 1H), 4.8-3.6 (m, 6H), 3.2-2.5 (m, 4H), 2.5-2.1 (m, 1H), 1.95 (three s, 3H), 1.9-1.3 (m, 6H), 1.1-0.7 (m, 6H).

K. N-[N-Acetyl-tyrosinyl-valinyl-(4-benzyloxy)prolinyl]-3-amino-4-oxobutanoic acid.

Step A. N-(N-Allyloxycarbonyl-4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by the reaction of N-allyloxycarbonyl-4-benzyloxyproline and 3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (T.L. Graybill et. al., Abstracts of papers, 206th National Meeting of the American Chemical Society, Abstract MEDI-235. Chicago, IL. (1993)) under similar peptide coupling conditions as reported above (compound H; Step C).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (br. s, 1H), 7.85 (br. m, 1H), 7.4-7.2 (m, 5H), 7.15 (br. s, 1H), 6.55 (br. s, 1H), 5.9 (m, 1H), 5.1-4.9 (br. m, 2H), 4.65-4.4 (m, 4H), 4.2 (br. m, 1H), 3.75-3.5 (m, 2H), 2.75-2.55 (m, 2H), 2.5 (br. m, 1H), 2.25 (br. m, 1H) 1.4 (s, 9H).

Step B. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by reaction of N-acetyl-tyrosinyl-valine and N-(N-allyloxycarbonyl-4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone by reaction conditions reported for compound H, step A.

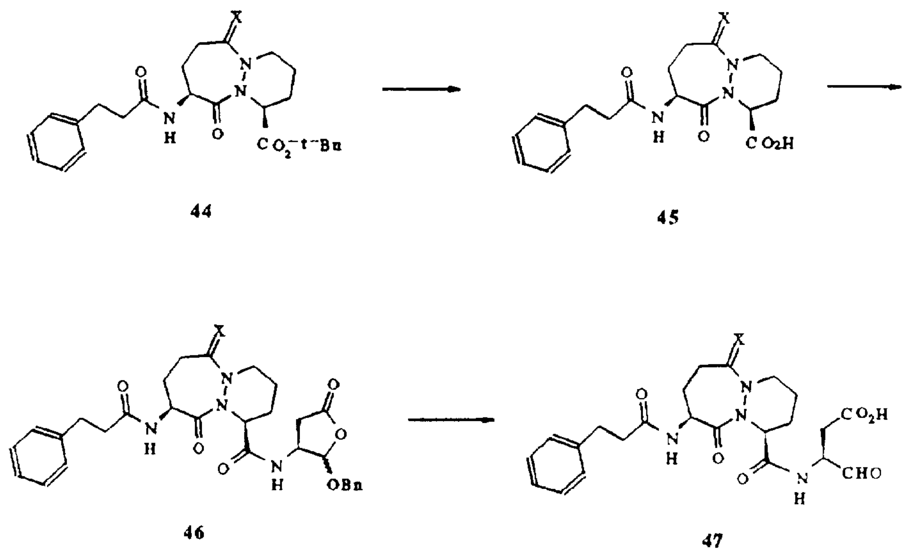
^{1}H NMR (500MHz, CD_3OD) δ 7.35-7.2 (m, 6H), 7.0 (d, 2H), 6.65(d, 2H), 4.85 (m, 1H), 4.6-4.45 (m, 4H), 4.3 (br. m, 1H), 4.15 (m, 1H), 3.7 (m, 1H), 2.95 (m,

IH), 2.75-2.6 (m, 3H), 2.35 (m, 1H), 2.1 (m, 1H), 1.9 (s, 3H), 1.4 (s, 9H), 0.95 (d, 3H), 0.90 (s, 3H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid.

N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (270 mg) was dissolved into 10 ml of 25% trifluoroacetic acid in dichloromethane and stirred at room temperature for 3 hours. The mixture was concentrated to give a solid residue. The residue was dissolved into a 10 ml mixture of methanol:acetic acid:37% formaldehyde (3:1:1) and stirred at room temperature for 1 hour. The mixture was concentrated and the resulting residue purified by flash chromatography (SiO_2) eluting with dichloromethane/methanol/formic acid (100:5:0.5) to give 37 mg of the title compound.

^1H NMR (500 MHz, CD_3OD (existing as a 1:1 mixture of diastereomers of the hemiacetal)) δ 7.4-7.25 (m, 5H), 7.0 (d, 2H), 6.65 (d, 2H), 4.65-4.05 (m, 7H), 3.75-3.4 (m, 2H), 3.05-2.3 (m, 5H), 2.2-1.95 (m, 2H), 1.90 (s, 3H), 1.0 (d, 3H), 0.95 (d, 3H).



(a) X = O

(b) X = H_2

(1*S*,9*S*) t-Butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44a). To a solution of (1*S*,9*S*) t-butyl 9-amino-6,10-dioxo-octahydro-6H-pyridazino [1,2-a][1,2]diazepine-1-carboxylate (690mg; 2.32mmol; GB 2128984) in dioxane (16ml) and water (4ml) at 0°C was added solid sodium bicarbonate (292mg; 3.48mmol) followed by dropwise addition of 3-phenylpropionyl chloride (470mg; 2.78mmol). The mixture was stirred at room temperature for 2h then more sodium bicarbonate (200mg; 2.38mmol) and 3-phenylpropionyl chloride (100mg; 0.6mmol) were added. The mixture was stirred for a further 2h at room temperature, diluted with ethyl acetate (50ml), washed with saturated sodium bicarbonate (2 x 25ml) then dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-50% ethyl acetate/chloroform)

and finally crystallized by trituration with ether to afford 860mg (86%) of a white solid: mp. 137-138°C; $[\alpha]_D^{23}$ -95.1° (c 0.549, CH_2Cl_2); IR (KBr) 3327, 1736, 1677, 1664, 1536, 1422, 1156; ^1H NMR ($CDCl_3$) δ 7.24 (5H, m), 6.50 (1H, d, J=7.5), 5.24 (1H, m), 4.90 (1H, m), 4.60 (1H, m), 3.44 (1H, m), 2.93 (2H, m), 2.84 (1H, m), 2.64 (1H, m), 2.54 (2H, m), 2.26 (2H, m), 1.70 (4H, m), 1.70 (9H, s). MS(FAB, m/z): 430 (M^+ + 1), 374, 242, 105, 91.

(1*S*,9*S*) t-Butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (44b), was prepared from (1*S*,9*S*) t-butyl 9-amino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (Attwood et al., J. Chem. Soc. Perkin 1, pp. 1011-19 (1986)) as for **44a**, to afford 810mg (81%) of a colorless oil: $[\alpha]_D^{23}$ - 33.5° (c 0.545, CH_2Cl_2); IR (film) 3334, 2935, 1737, 1728, 1659, 1642; ^1H NMR ($CDCl_3$) δ 7.24 (5H, m), 6.75 (1H, d, J=6.7), 5.27 (1H, m), 4.92 (1H, m), 3.39 (1H, m), 3.03 (4H, m), 2.55 (3H, m), 2.33 (1H, m), 2.17 (1H, m), 1.80 (5H, m), 1.47 (9H, s), 1.39 (1H, m). MS(FAB, m/z): 416 (M^+ + 1), 360, 211, 143, 97.

(1*S*,9*S*) 6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a). To a solution of (1*S*,9*S*) t-butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (**44a**) (800mg; 1.863mmol) in dry dichloromethane (5ml) at 0°C was added trifluoroacetic acid (5ml). The solution was stirred at room temperature for 3h then concentrated. Dry

ether (10ml) was added to the residue then removed under vacuum. This process was repeated three times to afford a crystalline solid. The solid was triturated with ether and filtered to afford 590mg (85%) of a white crystalline solid: mp. 196-197.5°C; $[\alpha]_D^{23}$ -129.5° (c 0.2, CH_3OH); IR (KBr) 3237, 1729, 1688, 1660, 1633, 1574, 1432, 1285, 1205; ^1H NMR (CD_3OD) δ 8.28 (1H, d, *J*=7.4), 7.22 (5H, m), 5.32 (1H, dd, *J*=5.9, 2.9), 4.75 (1H, m), 4.51 (1H, m), 3.50 (1H, m), 3.01 (1H, m), 2.91 (2H, m), 2.55 (2H, m), 2.29 (3H, m), 1.95 (2H, m), 1.71 (2H, m). Anal. Calcd for $C_{19}H_{23}N_3O_5$: C, 61.12; H, 6.21; N, 11.25. Found: C, 60.80; H, 6.28; N, 10.97. MS(FAB, m/z) 374 (M^+ + 1), 242, 105, 91.

(1*S*,9*S*) Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a]-[1,2]diazepine-1-carboxylic acid (45b), was prepared from (1*S*,9*S*) t-butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (**44b**) by the method described for compound **45a** to afford 657mg (96%) of **45b** as a crystalline solid: mp. 198-202°C; $[\alpha]_D^{23}$ -86.2° (c 0.5, CH_3OH); IR (KBr) 3294, 2939, 1729, 1645, 1620, 1574, 1453, 1214; ^1H NMR (CD_3OD) δ 7.92 (1H, d, *J*=7.9), 7.20 (5H, m), 5.29 (1H, m), 4.90 (1H, m), 3.47 (1H, m), 3.08 (2H, m), 2.90 (2H, m), 2.55 (3H, m), 2.36 (1H, m), 1.81 (5H, m), 1.43 (2H, m). MS(FAB, m/z) 360 (M^+ +1), 211,143,91.

[3*S*,2*R*,*S*,(1*S*,9*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46a). To a solution of (1*S*,9*S*) 6,10-dioxo-octahydro-9-(3-phenyl-propionylamino)-6H-pyridazino[1,2-a]

[1,2]diazepine-1-carboxylic acid (**45a**) (662mg; 1.773mmol) in dry dichloromethane (9ml) and dry dimethyl formamide (3ml) at room temperature was added bis(triphenylphosphine)palladium chloride (30mg) and (3*S*,2*R*,*S*)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) (568mg; 1.95mmol) followed by dropwise addition of tri-n-butyltin hydride (1.19g; 4.09mmol). 1-Hydroxy-benzotriazole (479mg; 3.546mmol) was added to the mixture and the mixture was cooled to 0°C before addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (408mg; 2.128mmol). The mixture was stirred at room temperature for 3.25h then diluted with ethyl acetate (50ml), washed twice with dilute hydrochloric acid (20ml), twice with saturated sodium bicarbonate (20ml), once with brine then dried ($MgSO_4$) and concentrated. The resulting oil was purified by flash chromatography (0-100% ethyl acetate/chloroform) to afford 810mg (81%) of **46a** as a mixture of anomers: mp. 92-94°C; IR (KBr) 3311, 1791, 1659, 1651, 1536; ^{1}H NMR($CDCl_3$) δ 7.49, 6.56 (1H, 2d, *J*=6.7, 7.8), 7.29 (10H, m), 6.37, 6.18 (1H, 2d, *J*=7.7,7.6), 5.56, 5.34 (1H, d, s, *J*=5.2), 5.08-4.47 (6H), 3.18-2.80 (5H), 2.62-2.28 (5H), 2.04-1.53 (5H). MS(FAB, m/z), 563 (M^+ + 1), 328, 149, 91.

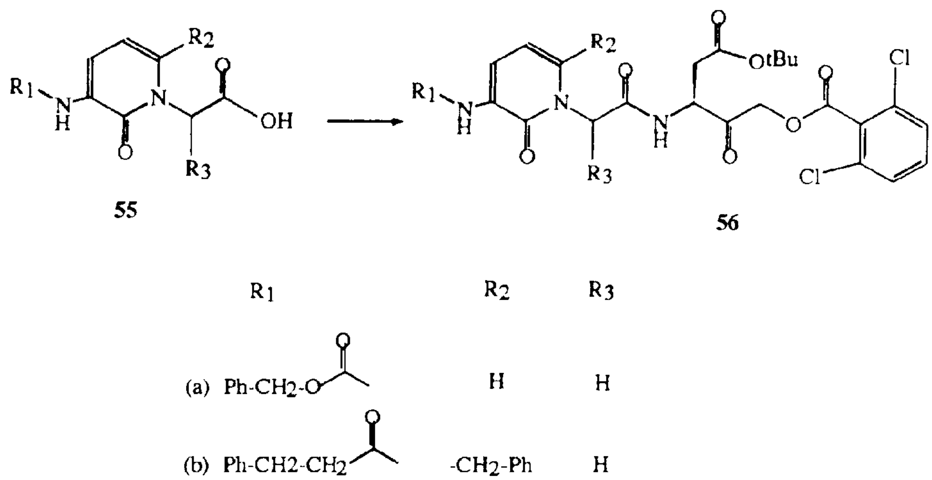
[3*S*,2*R*,*S*,(1*S*,9*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46b), was prepared from **45b** by the method described for **46a** to yield 790mg (96%) of a glass: m.p. 58-60°C; IR (KBr) 3316, 2940, 1793, 1678, 1641, 1523, 1453, 1120; ^{1}H NMR ($CDCl_3$) δ

7.28 (10H, m), 6.52, 6.42 (1H, 2d, *J*=7.2, 7.1), 5.53, 5.44 (1H, d, s, *J*=5.2), 5.35 (1H, m), 4.6-4.9, 4.34 (4H, m), 3.1-2.8 (6H, m), 2.6-2.1 (7H), 1.95-1.05 (5H). MS(FAB, m/z), 549 (M^+ + 1), 400, 310, 279, 91.

[3*S*(1*S*,9*S*)] 3-(6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47a). A mixture of [3*S*, 2*R*,*S*, (1*S*,9*S*)] N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**46a**) (205mg; 0.364mmol), 10% palladium on carbon (200mg) and methanol (20ml) was stirred under hydrogen at atmospheric pressure for 5h. The mixture was filtered then concentrated to yield 154mg (90%) of a glass: mp. 116-118°C; $[\alpha]_D^{23}$ -140° (c 0.1, CH_3OH); IR (KBr) 3323 (br), 1783, 1731, 1658, 1539, 1455, 1425; ^1H NMR (CD_3OD) δ 7.21 (5H, m), 5.17 (1H, m), 4.73 (1H, m), 4.50 (2H, m), 4.23 (1H, m), 3.38 (1H, m), 3.06 (1H, m), 2.91 (2H, m), 2.73-2.18 (6H, m) and 2.01-1.59 (5H, m). Anal. Calcd for $C_{23}H_{27}N_4O_7$ + H_2O : C, 56.32; H, 6.16; N, 11.42. Found: C, 56.29; H, 6.11; N, 11.25. MS(FAB, m/z) 473 (M^+ + 1), 176, 149, 105, 91.

[3*S*(1*S*,9*S*)]3-(Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47b), was prepared from **46b** by the method described for **47a**. The residue was purified by flash chromatography (0-10% methanol/chloroform) to afford 65mg (52%) of a glass; m.p. 87-90°C; $[\alpha]_D^{23}$ -167.0° (c 0.1, methanol); IR (KBr) 3329, 2936, 1786, 1727, 1637; ^1H NMR (CD_3OD) δ

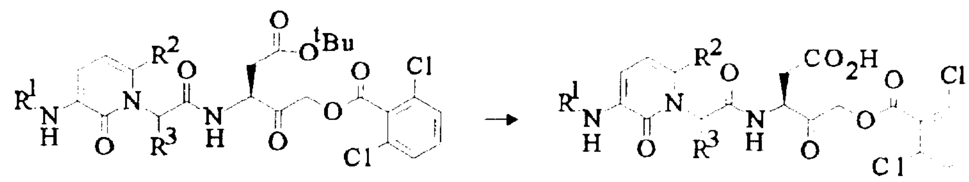
7.23 (5H, m), 5.29 (1H, m), 4.83 (1H, m), 4.59 (1H, d, *J*=3.6), 4.29 (1H, m), 3.3-3.0 (3H, m), 2.91 (2H, m), 2.70-2.34 (5H, m), 2.19 (2H, m), 1.75 (4H, m), 1.36 (2H, m). Anal. Calcd for $C_{23}H_{30}N_4O_6$ + $0.5H_2O$: C, 59.09; H, 6.68; N, 11.98. Found: C, 58.97; 6.68; N, 11.73. MS(FAB, m/z) 459 (M^+ + 1), 310, 149, 105, 91.



t-Butyl N-2-(3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1- pyridyl)acetyl-3-amino-5-(2,6-dichloro-benzoyloxy)-4-oxo-pentanoate (56a). The acetic acid **(55a)** (WO 93 21213) in THF (2ml) was stirred at room temperature and treated with 1-hydroxybenzotriazole (60mg, 0.448mmol) and dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (47mg, 0.246mmol). After 5 mins water (2 drops) was added and stirring continued for 20 minutes. Bis(triphenylphosphine) palladium II chloride (6mg) was added followed by a solution of t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoate (WO 93 16710) (103mg, 0.224mmol) in THF (1ml). Tributyltin hydride

(0.09ml, 0.336mmol) was added dropwise over 1 hour at room temperature. The mixture was stirred for a further 3 hours and poured onto ethyl acetate, washed with 1M HCl, aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with pentane and the supernatant discarded. The remaining solid was purified by flash chromatography (50% ethyl acetate/hexane) to afford the title compound 92mg (63%) as a colorless oil: $[\alpha]_D^{26}$ -29.6° (c 1.1, CH_2Cl_2); IR (film) 3377, 3365, 3332, 3312, 1733, 1691, 1650, 1599, 1515, 1366, 1261, 1153, 1068, 747; ^1H NMR ($CDCl_3$) δ 8.09 (1H, d, *J* = 6.8), 7.84 (1H, s), 7.58 (1H, d, *J* = 8.3), 7.33 (8H, m), 7.02 (1H, dd, *J* = 6.9, 1.7), 6.33 (1H, t, *J* = 7.2), 5.20 (2H, s), 5.12 (2H, m), 4.89 (1H, dt), 4.65 (2H, m), 2.80 (2H, m), 1.38 (9H, s).

t-Butyl N-2-(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzyloxy)-4-oxo-pentanoate (56b), was prepared by the method described for **(56a)** which afforded the title compound (66%) as a colorless oil: IR (film) 3364, 3313, 1738, 1688, 1648, 1600, 1566, 1514, 1433, 1369, 1254, 1152; ^1H NMR ($CDCl_3$) δ 8.40 (1H, d, *J* 7.6), 8.30 (1H, s), 7.28 (13H, m), 6.20 (1H, d, *J* = 7.6), 5.12 (2H, q), 4.86 (1H, m), 4.65 (2H, q), 4.06 (2H, s), 3.07-2.61 (6H, m), 1.39 (9H, s).



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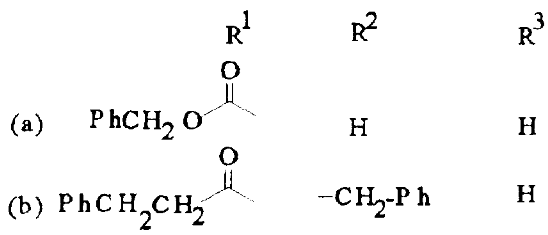
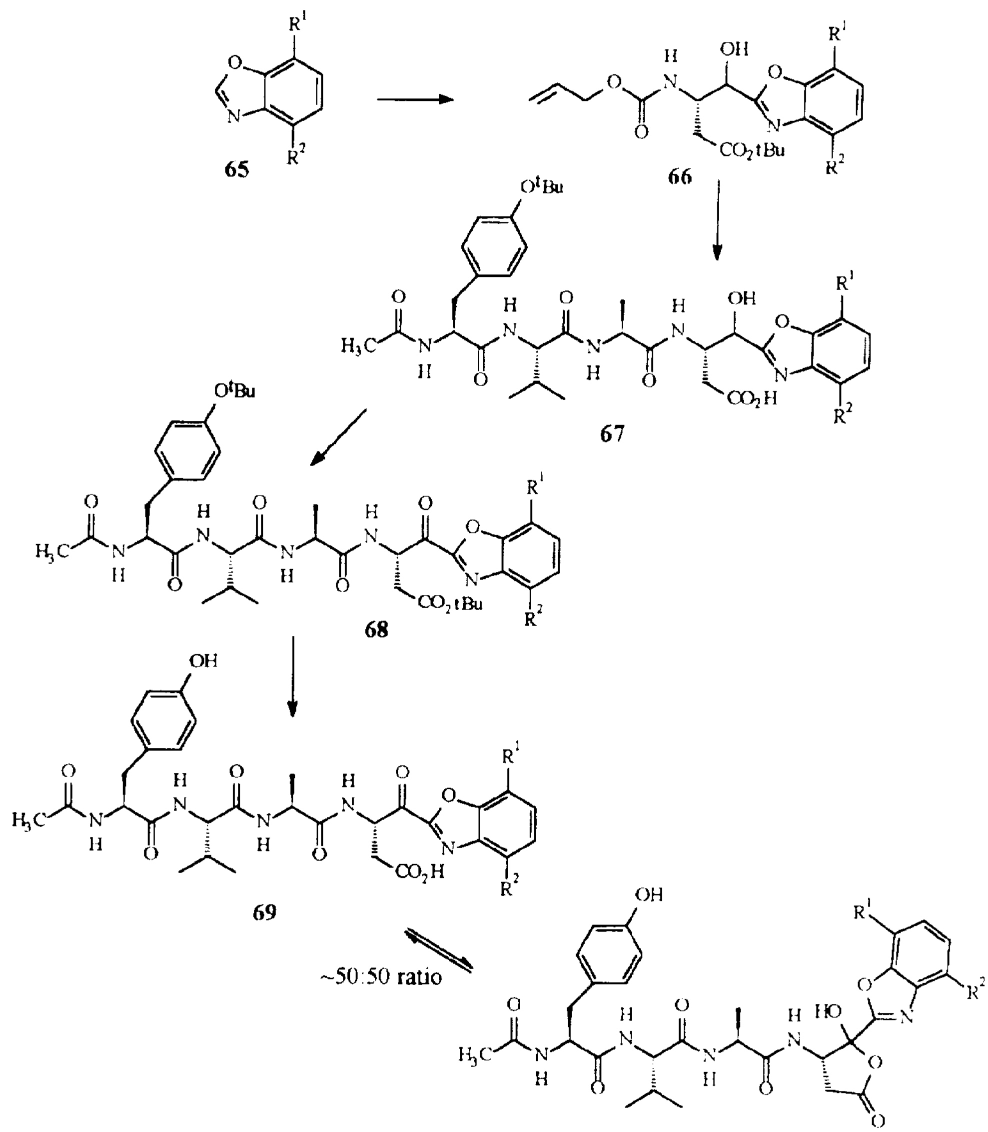


N-2(3-Benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (57a; Q). The ester **56a** (210mg, 0.356mmol) in dichloromethane (0.5ml) was cooled to 0°C and treated with trifluoroacetic acid (0.5ml), stirred and warmed to 20°C over 30 minutes. The solution was evaporated to dryness under reduced pressure, redissolved in dichloromethane and concentrated (x3). The residue was triturated with ethyl acetate and diluted with ether to afford the title compound 162mg (85%) as a colorless solid: m.p. 165-8°C (decomposition); $[\alpha]_D^{23}$ -38.8° (c 0.1, CH_3OH); IR (KBr) 3332, 3275, 1723, 1658, 1649, 1597, 1581, 1562, 1526, 1432, 1385, 1258, 1218, 1206; ^1H NMR (d_6-DMSO) δ 8.96 (1H, d, J = 7.3), 8.34 (1H, s), 7.85 (1H, dd, J = 7.3), 7.58 (3H, m), 7.35 (5H, m), 6.29 (1H, t, J = 7.3), 5.26 (2H, m), 5.15 (2H, s), 4.69 (3H, m), 2.75 (2H, m). Anal. Calcd. $C_{27}H_{23}N_3O_9Cl_2$: C, 53.66; H, 3.84; N, 6.95. Found: C, 53.36; H, 3.90; N, 6.81. M.S. (+ FAB); 604 (M^+ + 1), 285, 241, 195, 173, 149, 91.

N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl) amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichloro-benzoyloxy)-4-oxo-pentanoic acid (57b; P), was prepared by the method described for **57a** which afforded the title compound (78%) as colorless crystals: m.p. 116-120°C (decomposition); $[\alpha]_D^{26}$ -41.1° (c 0.1, CH_3OH); IR (KBr) 3299, 1739, 1715, 1689, 1666, 1645, 1598, 1563, 1518, 1432, 1209, 1151; ^1H NMR (d_6-DMSO) δ 9.24 (1H, s), 8.88 (1H, d, J = 7.6), 8.18 (1H, d, J = 7.7), 7.60 (3H, m), 7.26 (10H, m), 6.06 (1H, d, J = 7.7), 5.23 (2H, ABq), 4.69 (3H, m), 3.93 (2H, s), 2.78 (6H, m). Anal. Calcd. for $C_{35}H_{31}N_3O_8Cl_2$. H_2O: C, 59.16; H, 4.68; N, 5.91. Found: C, 59.38; H, 4.53; N, 5.84. M.S. (+ FAB); 694, (Cl=35, 37), (M^+ + 1); 692 (Cl=35, 35), (M^+ + 1).



(a) $R^1 = OCH_3$, $R^2 = H$

(b) $R^1 = H$, $R^2 = OCH_3$

7-Methoxybenzoxazole (65a). A mixture of 2-nitro-6-methoxyphenol (2.62g, 15.5mmol) (EP 333176) and 10% Palladium on carbon (130mg) in ethanol (50.0ml) was stirred under an atmosphere of H_2 for 75min. The

mixture was filtered through Celite® then immediately treated with *p*-toluenesulphonic acid (32.0mg) and triethylorthoformate (6.45ml, 38.8mmol) then heated under reflux under an atmosphere of N_2. After 20h *p*-toluenesulphonic acid (30.0mg) and triethylorthoformate (6.45ml, 38.8mmol) were added. After a total of 44h heating, the reaction was allowed to cool and reduced *in vacuo*. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 1.97g (85%) of the title compound as a yellow solid: m.p. 28-31°C; IR (film) 1629, 1497, 1434, 1285, 1097; ^1H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.40 (1H, d, *J* = 8.0), 7.28 (1H, t, *J* = 8.0), 6.89 (1H, d, *J* = 8.0), 4.02 (3H, s); ^{13}C NMR ($CDCl_3$) δ 152.84, 145.82, 142.50, 139.99, 125.75, 113.42, 108.80, 56.97. Anal. Calcd. for $C_8H_7N_1O_2$. $0.1H_2O$: C, 63.65; H, 4.81; N, 9.29. Found: C, 63.43, H, 4.88, N, 9.05. M.S. (+ FAB); 150 (M^+ + 1).

4-Methoxybenzoxazole (65b). To a suspension of 4-hydroxybenzoxazole (2.00g, 14.8mmol) (Musser et al., J. Med. Chem., 30, pp. 62-67 (1987)) in acetone (80.0ml) was added dried K_2CO_3 (2.25g, 16.3mmol) followed by iodomethane (1.38ml, 22.2mmol). The reaction was heated under reflux under N_2 for 4.5h, then filtered and reduced *in vacuo* to afford the crude product. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 2.0g (91%) of the title compound as a white crystalline solid: m.p. 72-74°C; IR (KBr) 3089, 1619, 1610, 1503, 1496, 1322, 1275, 1090, 1071, 780, 741; ^1H NMR ($CDCl_3$) δ 8.02 (1H, s), 7.32 (1H, t, *J* = 8.0), 7.18 (1H, d, *J*= 8.0), 6.81 (1H, d, *J* = 8.0), 4.04 (3H, s). Anal. Calcd. for

$C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.40; H, 4.84; N, 9.31; m/z (EI) 149 (M^+ + 1, 100%).

(3*S*, 4*R*,*S*) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (66a). To a stirred solution of 7-methoxybenzoxazole **65a** (548.6mg, 3.68mmol) in anhydrous THF (18.5ml) at -78°C under N_2 was added 1.56M *n*-butyl lithium in hexanes (2.47ml, 3.86mmol) dropwise, to produce a yellow colored solution. After stirring at -78°C for 20 min, dry $MgBr_2OEt_2$ (1.045g, 4.05mmol) was added as a solid. The resulting heterogeneous mixture was warmed to -45°C and stirred for 15min. The reaction mixture was then recooled to -78°C and a solution of (S)-Alloc-Asp(*t*-Bu)H (946.4mg, 3.68mmol) in THF (18.5ml) was added dropwise. The reaction was stirred at -78°C for 30min, warmed to 0°C and stirred for 1h. The resulting homogeneous reaction was warmed to room temperature and stirred for 16h. The reaction was quenched with 5% sodium bicarbonate (3.5ml) then THF was removed *in vacuo*. The resulting aqueous residue was extracted with methylene chloride (x6). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and reduced *in vacuo* to give 1.8g of crude product. Flash chromatography (40:60 ethyl acetate/hexane) gave 1.21g (81%) of the title compound, an oil, as a mixture of diastereoisomers at C-4: IR (CH_2Cl_2) 3425, 2983, 1725, 1504, 1290, 1157, 1101; ^1H NMR ($CDCl_3$) δ 7.35-7.19 (2H, m), 6.89-6.81 (1H, m), 6.00-5.57 (2H, m), 5.32-5.05 (3H, m), 4.68-4.35 (3H, m), 4.01 (3H, s), 2.86-2.59 (2H, m), 1.45 (9H, s), 1.41 (9H, s); ^{13}C NMR ($CDCl_3$) δ 171.18, 171.09, 165.80, 165.30, 156.71, 156.60, 145.65, 142.76, 142.71, 140.82, 140.72, 133.23, 125.81, 125.72,

118.41, 118.21, 113.07, 112.87, 108.95, 82.16, 70.28, 69.98, 66.52, 66.39, 57.03, 52.57, 52.29, 37.83, 36.86, 28.65. Anal. Calcd. for $C_{20}H_{26}N_2O_7$. $0.6H_2O$: C, 57.57; H, 6.57; N, 6.72. Found: C, 57.49, H, 6.34, N, 6.60. M.S. (+ FAB); 407 (M^+ + 1); 351, 307, 154.

(3*S*, 4*R,S*) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (66b), was prepared according to the method described for **66a** which afforded 1.29g (26%, 68% based on recovered starting material) of the title compound as an oil and as a mixture of diastereoisomers at C-4: IR (CH_2Cl_2) 3400, 1725, 1625, 1505, 1369, 1354, 1281, 1263, 1226, 1158, 1092, 1048; ^{1}H NMR ($CDCl_3$) δ 7.34-7.24 (1H, m), 7.16 (1H, d, J = 8.2), 6.79 (1H, d, J = 7.9), 6.00-5.50 (2H, m), 5.30-5.05 (3H, m), 4.70-4.35 (4H, m), 4.02 (3H, s), 2.90-2.45 (2H, m), 1.45-1.41 (9H, 2 x s). Anal. Calcd. for $C_{20}H_{26}N_2O_7$. $0.4H_2O$: C, 58.07; H, 6.53; N, 6.77. Found: C, 58.09; H, 6.41; N, 6.63. M.S. (+ FAB); 407 (M^+ + 1, 88%); 351 (100).

(3*S*, 4*R,S*) t-Butyl N-(N-acetyl-(*S*)-(O-tert-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (67a). To a stirred solution of the benzoxazole **66a** (481.9mg, 1.19mmol) and Ac-Tyr(^{t}Bu)-Val-Ala-OH (586.3mg, 1.30mmol) in methylene chloride (3.5ml) and DMF (3.5ml) was added bis(triphenylphosphine) palladium (II) chloride (18.0mg), followed by tributyltinhydride (0.80ml, 2.96mmol) dropwise. Hydroxybenzotriazole (320.4mg, 2.37mmol) was added and the mixture cooled to 0°C. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (278.2mg, 1.42mmol) was added and the

mixture was allowed to warm to room temperature and stirred for 16.5h. The reaction was diluted with ethyl acetate and washed twice with 1M sodium hydrogensulphate, twice with saturated sodium bicarbonate, water, and brine. The organic layer was dried ($MgSO_4$), filtered and reduced *in vacuo* to yield 2.0g of crude product. Flash chromatography (95:5 methylene chloride/methanol) gave 844.0mg (94%) of the title compound as a white solid: m.p. 205°C; IR (KBr) 3399, 3304, 2977, 1729, 1643, 1506, 1367, 1290, 1161; ^{1}H NMR (d_6-DMSO) δ 8.24-7.78 (4H, m), 7.43-7.32 (2H, m), 7.23 (2H, d, *J* = 8.5), 7.16-7.07 (1H, m), 6.93 (2H, d, *J* = 8.5), 6.52, 6.40 (1H, 2 x d, *J* = 5.5, *J*= 5.0), 5.03, 4.78-4.49, 4.45-4.16 (5H, brt, 2 x m), 4.05, 4.04 (3H, 2 x s), 3.08-2.35 (14H, m), 2.11-1.89 (1H, m), 1.83 (3H, s), 1.49-1.32, 1.15, 1.0-0.81 (27H, s, 2 x m, *J* = 7.0); ^{13}C NMR (d_6-DMSO) δ 175.55, 175.18, 173.88, 173.75, 173.05, 169.23, 157.28, 148.55, 146.16, 143.21, 136.63, 133.55, 128.87, 127.17, 115.78, 111.92, 84.02, 81.50, 71.40, 61.15, 60.05, 57.79, 53.39, 51.62, 43.76, 40.52, 34.58, 32.52, 31.60, 26.35, 23.11, 22.71, 21.76. Anal. Calcd. for $C_{39}H_{55}N_5O_{10}$. $0.5H_2O$: C, 61.40; H, 7.40; N, 9.18. Found: C, 61.43; H, 7.31; N, 9.07. M.S. (+ FAB); 754 (M^+ + 1); 698, 338, 267.

(3*S*, 4*R*,*S*) t-Butyl N-(N-acetyl-(*S*)-(O-tert-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (67b), was prepared according to the method described for **67a** which afforded 1.05g (94%) of the title compound as a fine white powder: m.p. 210-213°C (dec); IR (KBr) 3284, 2977, 1736, 1691, 1632, 1536, 1505, 1452, 1392, 1367, 1258, 1236, 1161, 1091; ^{1}H NMR (d_6-DMSO) δ 8.20-

7.75 (4H, m), 7.40-7.10 (4H, m), 7.00-6.80 (3H, m), 6.45, 6.34 (1H, 2 x d, *J* = 5.3, *J* = 5.0), 5.00-4.10 (5H, m), 4.00, 3.99 (3H, 2 x s), 3.00-2.25 (4H, m), 1.95 (1H, m), 1.78 (3H, s), 1.39-0.80 (27H, m). Anal. Calcd. for $C_{39}H_{55}N_5O_{10}$. $0.5H_2O$: C, 61.40; H, 7.40; N, 9.18. Found: C, 61.58; H, 7.38; N, 8.91. M.S. (+ FAB); 754 (M^+ + 1, 30%); 72 (100).

(3*S*) t-Butyl N-(N-acetyl-(*S*)-(O-tert-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (68a). The Dess-Martin reagent (1.082g, 2.55mmol) (Ireland et al., J. Org. Chem., 58, p. 2899 (1993); Dess et al., J. Org. Chem., 48, pp. 4155-4156 (1983)) was added to a stirred suspension of the alcohol **67a** (641.0mg, 0.85mmol) in methylene chloride (46.0ml). The resulting mixture was stirred for 1h before being partitioned between saturated sodium thiosulphate: saturated sodium bicarbonate (1:1, 86.0ml) and ethyl acetate (86.0ml). The resultant organic phase was washed in turn with saturated sodium thiosulphate: saturated sodium bicarbonate (1:1), saturated sodium bicarbonate, and brine. The organic phase was dried ($MgSO_4$), filtered and reduced *in vacuo* to give 660.0mg of crude product. Flash chromatography (94:6 methylene chloride/methanol) gave 636.0mg (100%) of the title compound as a white solid: m.p. 209°C; $[\alpha]_D^{24}$ -21.8° (c 0.16, methanol); IR (KBr) 3395, 3294, 2977, 1722, 1641, 1535, 1505, 1161; ^{1}H NMR ($CDCl_3$) δ 8.43-8.16 (1H, m), 7.97-7.62 (2H, m), 7.49-7.14 (3H, m), 7.08-6.95 (3H, m), 6.89-6.73 (2H, m), 5.81-5.68 (1H, m), 5.16-4.86 (2H, m), 4.53 (1H, brt), 4.03 (3H, s), 3.16-2.84 (4H, m), 2.11-1.84 (4H, m), 1.46-1.14 (21H, m), 0.92-0.78 (6H, m); ^{13}C NMR

($CDCl_3$) δ 186.28, 173.39, 171.90, 171.19, 171.03, 169.89, 156.43, 154.75, 146.32, 142.88, 140.98, 132.31, 130.54, 126.98, 124.73, 114.95, 111.42, 82.44, 78.71, 58.92, 57.20, 54.91, 53.47, 48.77, 39.43, 38.15, 32.79, 29.44, 28.60, 23.55, 20.27, 19.70, 19.34. M.S. (+ FAB); 752 (M^+ + 1); 696, 336, 265.

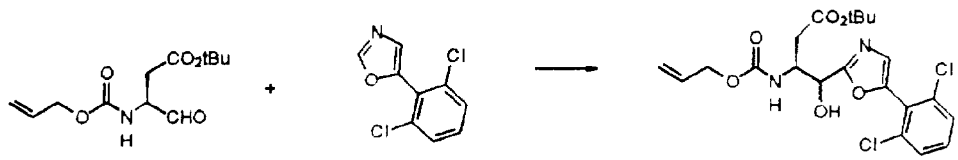
(3*S*) t-Butyl N-(N-acetyl-(*S*)-(O)-tert-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (68b), was prepared according to the method described for the ketone **68a** which afforded 420mg (55%) of the title compound as a white solid: m.p. 211-213°C (dec); $[\alpha]_D^{24}$ -23.9° (c 0.82, methanol); IR (KBr) 3277, 3075, 1723, 1690, 1632, 1530, 1506, 1392, 1366, 1269, 1234, 1160, 1094; ^{1}H NMR ($CDCl_3$) δ 8.15 (1H, brs), 7.7 (2H, brs), 7.46 (1H, t, *J* = 8.3), 7.24 (2H, d, *J* = 8.3), 7.10 (1H, brs), 7.03 (2H, d, *J* = 8.3), 6.83 (3H, m), 5.74 (1H, q, *J* = 6.9), 5.00 (2H, m), 4.51 (1H, t, *J* = 7.0), 4.07 (3H, s), 3.20-2.95 (4H, m), 2.00 (4H, m), 1.42 (3H, d, *J* = 6.8), 1.35 (9H, s), 1.23 (9H, s), 0.86 (6H, d, *J* = 6.7). M.S. (+ FAB); 752 (M^+ + 1, 7%); 72 (100).

(3*S*) N-(N-Acetyl-(*S*)-tyrosinyl-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (69a; R). A solution of the ester **68a** (600.0mg, 0.80mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (65.0ml) was stirred for 1h under a dry atmosphere of N_2. The solution was then reduced *in vacuo*, taken up in ether and reduced again. This process was repeated six times to afford the crude product as an off white solid. Flash chromatography (gradient 95:5 to 80:20 methylene

chloride/methanol) gave 420.8mg (83%) of the title compound as a hygroscopic white solid. The product existed as a mixture of three isomers in CD_3OD, consisting of the keto form (c 50%), and its acycloxy keto form (two isomers at C-4, c 50%): m.p. decomposes above 150°C; $[\alpha]_D^{24}$-33.2° (c 0.17, methanol); IR (KBr) 3300, 1715, 1658, 1650, 1531, 1517, 1204; ^{1}H NMR (CD_3OD) δ 7.46-7.19 (2H, m), 7.16-6.91 (3H, m), 6.70-6.59 (2H, m), 5.62-5.49 (1H, m), 5.00-4.72 (1H, obscurred m), 4.69-4.51 (1H, m), 4.49-4.08 (2H, m), 4.05-3.89 (3H, m), 3.16-2.47 (4H, m), 2.05-1.78 (4H, m), 1.41-1.11, 1.05-0.70 (9H, 2 x m). Anal. Calcd. for $C_{31}H_{37}N_5O_{10}$. $3H_2O$: C, 53.67; H, 6.25; N, 10.10. Found: C, 53.76; H, 5.56; N, 10.28. M.S. (+ FAB); 640 (M^+ + 1); 435, 147.

(3*S*) t-Butyl N-(N-acetyl-(*S*)-tyrosinyl-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (69b; S), was prepared according to the method described for the acid **69a** which afforded the hygroscopic title compound 252mg (96%). The product existed as a mixture of three isomers in CD_3OD, consisting of the keto form, and its acycloxy ketal form (two isomers at C-4). The product existed as a single isomer in d-6 DMSO: m.p. 200-203°C (dec.); $[\alpha]_D^{24}$ -38.0° (c 0.23, methanol); IR (KBr) 3289, 2968, 1718, 1713, 1658, 1634, 1548, 1517, 1506, 1461, 1453, 1393, 1369, 1268, 1228, 1174, 1092; ^{1}H NMR (d_6-DMSO) δ 9.20 (1H, brs), 8.71 (1H, d, *J* = 6.2), 8.10 (2H, m), 7.83 (1H, d, *J* = 8.7), 7.61 (1H, t, *J* = 8.2), 7.46 (1H, d, *J* = 8.2), 7.08 (3H, m), 6.65 (2H, d, *J* = 8.3), 5.50 (1H, q, *J* = 6.5), 4.50 (1H, m), 4.37 (1H, m), 4.20 (1H, m), 4.05 (3H, s), 3.09-2.77 (4H, m), 1.94 (1H, m), 1.79

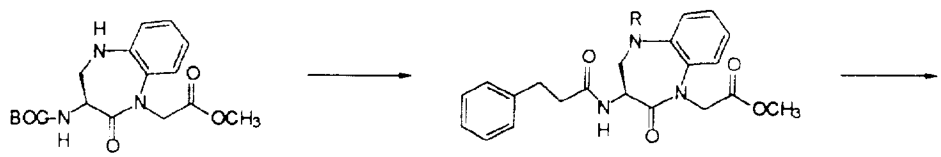
(3H, s), 1.23 (3H, d, J = 7.0), 0.82 (6H, m). Anal. Calcd. for $C_{31}H_{37}N_5O_{10}$. $1.5H_2O$: C, 55.85; H, 6.05; N, 10.51. Found: C, 55.21; H, 5.69; N, 10.13. M.S. (+ FAB); 640 (M^+ + 1, 22%); 107 (100).



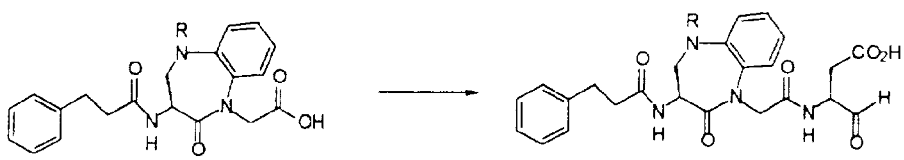
58 99

3(*S*)-(Allyloxycarbonyl)-amino-4-[(2,6-dichloro-phenyl)-oxazol-2-yl]-4(*R,S*)-hydroxy-butyric acid tert-butyl ester (99). A solution of 5-(2,6-Dichlorophenyl)oxazole (2.71g, 12.7mmol; prepared by a similar method described in Tet. Lett. 23, p. 2369 (1972)) in tetrahydrofuran (65mL) was cooled to -78 °C under a nitrogen atmosphere. To this solution was added n-butyl lithium (1.5M solution in hexanes, 8.5mL, 13.3mmol) and stirred at -78 °C for 30min. Magnesium bromide etherate (3.6g, 13.9mmol) was added and the solution was allowed to warm to -45 °C for 15min. The reaction was cooled to -78 °C and aldehyde **58** (3.26g, 12.7mmol; Graybill et al., Int. J. Protein Res., 44, pp. 173-182 (1993)) in tetrahydrofuran (65mL) was added dropwise. The reaction was stirred for 25min., then allowed to warm to -40 °C and stirred for 3h, and then at room temperature for 1h. The reaction was quenched with 5% $NaHCO_3$ (12mL) and stirred for 3h. The tetrahydrofuran was removed in vacuo and the resulting residue was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride solution and dried over magnesium sulfate, filtered, and concentrated to yield 6.14g of the title compound.

Purification gave 4.79g (80%) of **99**: ^{1}H NMR ($CDCl_3$) δ 1.45(s, 9H), 2.7-2.5(m, 2H), 2.8(dd, 1H), 4.2, 4.4(2 x d, 1H), 4.7-4.5(m, 3H), 5.35-5.1(m, 2H), 5.6, 5.7(2 x d, 1H), 6.0-5.8(m, 1H), 7.2(d, 1H), 7.3(m, 1H), 7.4(m, 2H).



103 **104**



105 **106**

a R = H

b R = $COCH_2CH_2Ph$

c R = CH_2Ph

[2-Oxo-3(*S*)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104a). Anhydrous hydrogen chloride was bubbled into a solution of (3(S)-*tert*-butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (**103**, 1g, 2.86 mmol) in 25 ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-

tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid.
The hydrochloride salt and hydrocinnamic acid (0.47 g, 3.15 mmol) were dissolved into 20 ml of dimethylformamide and cooled to 0 °C. Diisopropylethylamine (1 ml, 5.72 mmol) was added to the solution followed by the addition of N-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring for 18 hours at room temperature, the mixture was diluted with 150 ml of ethyl acetate and washed with 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to a crude solid that was purified by flash chromatography eluting with 7:3 ethyl acetate/dichloromethane to afford 600 mg (55%)of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.3-6.85 (9H,m), 6.55-6.0 (1H, d), 4.88-4.82 (1H, m), 4.72-4.65 (1H, d), 4.28-4.22 (1H, m), 3.95-3.9 (1H, m), 3.78 (3H, s), 3.65 (1H, br. s), 3.28-3.2 (1H, m), 2.95-2.84 (2H, m), 2.55-2.4 (2H, m).

(3(*S*)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid (105a).
(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetrahydro-benzo[b] [1,4]diazepin-1-yl)acetic acid methyl ester (**104a**) was dissolved in 90% methanol. Lithium hydroxide hydrate was added to the reaction and the reaction was stirred at room temperature for 4 h. The reaction was evaporated in vacuo to give a white solid. This was dissolved in 20 ml of water and acidified to pH 5 and extracted with ethyl acetate to afford 304 mg (88%) of the title compound as a white

solid. ^1H NMR ($CDCl_3$) δ 7.5-6.9 (11H, m), 4.92-4.8 (1H, m), 4.7-4.58 (1H, d), 4.38-4.25 (1H, d), 3.88-3.78 (1H, m), 3.45-3.25 (1H, m), 3.05-2.85 (2H, m), 2.55-2.45 (2H, m).

4-Oxo-3(*S*)-{2-[2-oxo-3(*S*)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-ylacetylamino}butyric acid (106a). N-[1-(2-Benzyloxy-5-oxotetrahydrofuran-3-ylcarbamoyl-methyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-3-phenylpropionamide was prepared from **105a** by the procedure used to prepare compound **H** (stepA) to afford 390 mg (93%) of the product as diastereomers. ^1H NMR (CD_3OD) δ 7.58-7.22 (14H, m), 5.78-5.73 (0.5 H, d), 5.64 (0.5 H, s), 5.0-4.72 (4H, m), 4.54-4.42 (2H, m), 3.82-3.76 (0.5 H, m), 3.68-3.62 (o.5 H, m), 3.28-3.21 (0.5H, m), 3.19-3.12 (0.5H, m), 3.07-2.98 (2H, m), 2.78-2.48 (4H, m).

The resulting product was converted to **106a** by the method described to prepare compound **H** (StepD) to afford the title compound as a white solid (17%): ^1H NMR (CD_3OD) δ 7.54-6.98 (9H, m), 5.58-5.44 (1H, m), 4.8-4.2 (4H, m), 3.96-3.3 (2H, m), 3.30-3.05 (1H, m), 2.98-2.25 (5H, m).

[2-Oxo-5-(3-phenylpropionyl)-3(*S*)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104b). Anhydrous hydrogen chloride was bubbled into a solution of (3(S)-*tert*-butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (**103**, 1g, 2.86mmol) in 25

ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid. The hydrochloride salt was suspended into 20 ml of dichloromethane and cooled to 0 °C. Triethylamine (1.6 ml, 11.5 mmol) was added to the suspension followed by the dropwise addition of dihydrocinnamoyl chloride (0.9 ml, 6 mmol). The mixture was warmed to room temperature and stirred for 18 hours. The mixture was diluted with 25 ml of dichloromethane and washed twice with 50 ml of water and once with 50 ml of brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with 1:1 ethyl acetate/dichloromethane to afford 1.35 g (92%) of the title product as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.45-7.02 (14 H, m), 6.37-6.32 (1H, d), 4.78-4.72 (1H, m), 4.52-4.3 (3H, m), 3.82-3.77 (1H,m), 3.74 (3H, s), 3.03-2.87 (4H, m), 2.58-2.45 (2H, m), 2.45-2.35 (1H, m), 2.25-2.16 (1H, m).

[2-Oxo-5-(3-phenylpropionyl)-3-(3(*S*)-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid (105b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (**104b**; 680 mg, 1.32 mmol) was hydrolyzed by the procedure used to hydrolyze **105a** to afford 645 mg (98%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.58 (1H, br. s), 7.5-7.42 (1H, m), 7.35-6.95 (14H,

m), 4.95-4.88 (1H, m), 4.64-4.55 (1H, d), 4.54-4.45 (1H, t), 4.15-4.05 (1H, d), 3.75 (1H, m), 3.05-2.75 (4H, m), 2.58-2.45 (2H, m), 2.45-2.28 (1H, m), 2.25-2.14 (1H, m).

2-Oxo-3(*S*)-{2-[2-oxo-5-(3-phenylpropionyl)-3(*S*)-(3-phenyl-propionyl-amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl] acetylamino}butyric acid (106b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid and 3-amino-4-oxobutyric acid tert-butylester semicarbazone were coupled by the procedure used in the preparation of compound **K** (step A) to give 350 mg (85%) of a white solid. ^{1}H NMR ($CDCl_3$) δ 9.05 (1H, br. s), 7.58-7.55 (1H,d), 7.5-7.35 (1H, m), 7.35-6.95 (14 H, m), 6.75-6.72 (1H, d), 6.25 (1H, br. s), 5.25 (1H, br. s), 4.95-4.88 (1H, m), 4.8-4.72 (1H, m), 4.55-4.4 (2H, m), 3.92-3.88 (1H, d), 3.73-3.68 (1H, m), 2.95-2.8 (4H, m), 2.8-2.72 (1H, m), 2.62-2.55 (1H, m), 2.55-2.45 (2H, m), 2.4-2.32 (1H, m), 2.2-2.12 (1H, m), 1.45 (9H, s). 4-Oxo-3-{2-[2-oxo-5-(3-phenylpropionyl)-3-(3-phenyl-propionyl -amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetyl-amino}butyric acid tert-butyl ester semicarbazone was deprotected as described in the preparation of compound K (step C) to give 118 mg (47%) of the title compound as a white solid. ^{1}H NMR (CD_3OD) δ 7.48-6.95 (14 H, m), 4.65-4.15 (6H, m), 3.5-3.4 (1H, m), 2.85-2.72 (4H, m), 2.65-2.5 (1H, m), 2.5-2.34 (3H, m), 2.34-2.15 (2H, m).

[5-Benzyl-2-oxo-3(*S*)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid

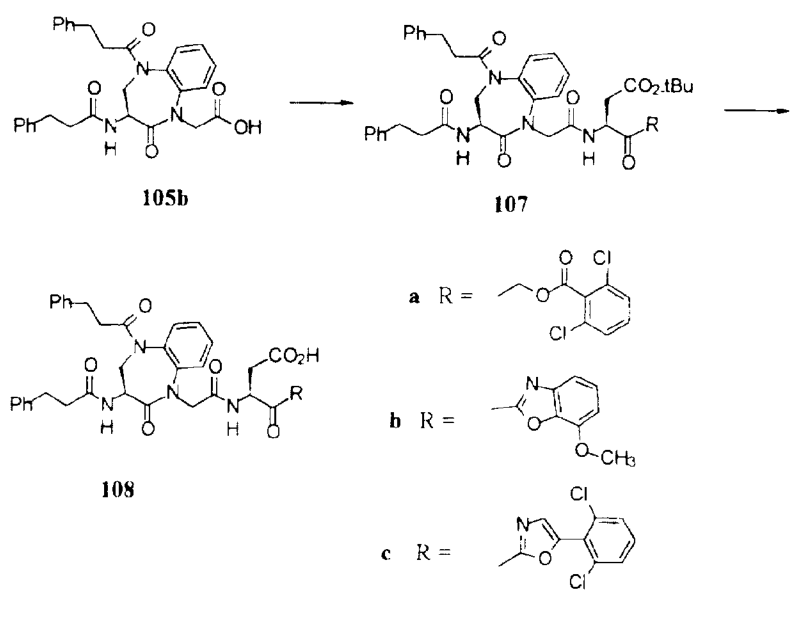
methyl ester (104c). [2-Oxo-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo-[b][1,4]diazepin-1-yl]acetic acid methyl ester (**104a**; 500 mg, 1.31 mmol), calcium carbonate (155 mg, 1.58 mmol), and benzyl bromide (170 µl, 1.44 mmol) were taken into 10 ml of dimethylformamide and heated to 80 °C for 8 hours. The mixture was diluted with 150 ml of ethyl acetate and washed 4 times with 50 ml of water. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with dichloromethane/ethyl acetate (8:2) to give 460 mg (75%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.34-7.05 (14 H, m), 6.32-6.28 (1H, d), 4.84-4.76 (1H, d), 4.76-4.70 (1H, m), 4.43-4.37 (1H, d), 4.26-4.18 (1H, d), 4.06-4.00 (1H, d), 3.79 (3H, s), 3.45-3.37 (1H, m), 3.02-2.95 (1H, m), 2.90-2.82 (2H, m), 2.5-2.34 (2H, m).

[5-Benzyl-2-oxo-3(*S*)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid (105c) was prepared by the hydrolysis of the ester (**102c**) by the procedure reported in Example **105a** to give 450 mg (98%) of the title compound as a white solid: ^{1}H NMR (CD_3OD) δ 7.5-7.05 (14 H, m), 6.4 (1H, br. s), 4.85-4.55 (2H,m), 4.5-4.21 (2H, m), 4.12-3.92 (1H, d), 3.45-3.3 (1H, m), 3.1-2.8 (3H, m), 2.55-2.28 (3H, m).

3(*S*)-{2-[5-Benzyl-2-oxo-3-(3(*S*)-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino}-4-oxobutyric acid (106c). [5-Benzyl-2-

oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b[1,4]diazepin-1-yl]acetic acid and 3(S)-amino-4-oxobutyric acid tert-butylester semicarbazone were coupled by the procedure used in the preparation of compound **K** (step A) and to afford 260 mg (85%) of a white solid: ^{1}H NMR (CD_3OD) δ 7.35-7.0 (15 H, m), 4.94-4.88 (1H, m), 4.68-4.58 (1H, d), 4.57-4.52 (1H, m), 4.41-4.34 (1H, d), 4.3-4.23 (1H, d), 4.1-4.04 (1H, d), 3.18-3.11 (1H, m), 3.09-2.98 (1H, m), 2.78-2.72 (2H, t), 2.65-2.57 (1H, m), 2.42-2.33 (3H, m).

3(S)-{2-[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino}-4-oxobutyric acid tert-butyl ester semicarbazone was deprotected as described in the preparation of compound K (step C) to give 168 mg (81%) of the title compound as a white solid. ^{1}H NMR (CD_3OD) δ 7.37-7.0 (14H, m), 4.75-4.62 (1H, m), 4.6-4.45 (2H, m), 4.4-4.21 (2H, m), 4.15-3.95 (2H, m), 3.15-3.0 (2H, m), 2.82-2.67 (2H, m), 2.65-2.52 (1H, m), 2.5-2.32 (3H, m).

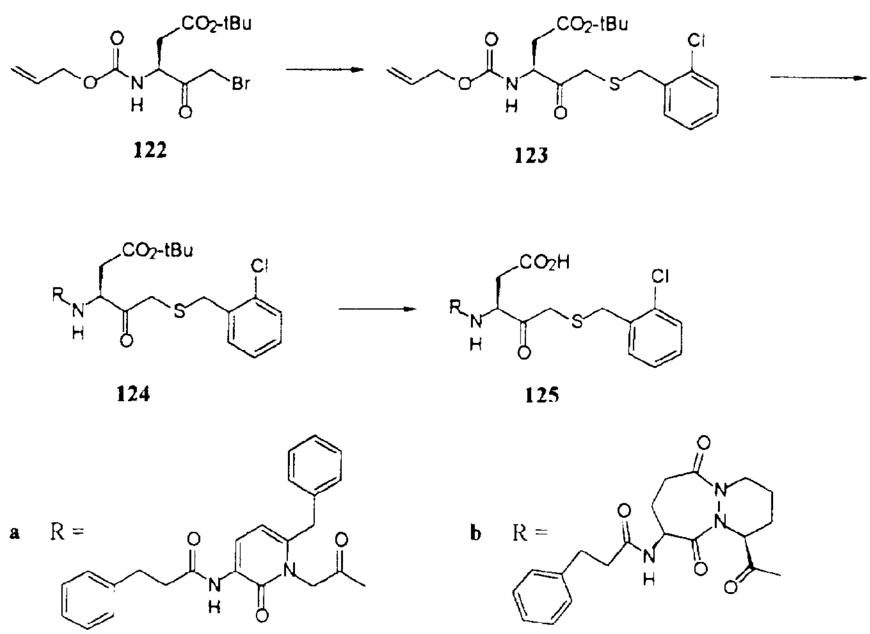


2,6-Dichlorobenzoic acid 4-tert-butoxycarbonyl-2-oxo-3(*S*)-{2-[2-oxo-5-(3-phenylpropionyl)-3(*S*)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetyl-amino}butyl ester (107a). The resulting semicarbazone was prepared by the coupling of compound **105b** and t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoate (WO 93 16710) as described in compound **56a** to give 256 mg (58%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.45-7.04 (17H, m), 6.45-6.34 (2H, m), 5.28-5.21 (1H, m), 5.1-5.0 (1H, m), 4.95-4.90 (1H, m), 4.75-4.70 (1H, m), 4.55-4.44 (1H, m), 4.32-4.22 (1H, dd), 3.99-3.85 (1H, dd), 3.85-3.76 (1H, m), 3.06-2.83 (5H, m), 2.83-2.74 (1H, m), 2.6-2.44 (2H, m), 2.43-2.33 (1H, m), 2.24-2.15 (1H, m), 1.45 (9H, s).

2,6-Dichlorobenzoic acid 4-carboxy-2-oxo-3(*S*)-{2-[2-oxo-5-(3-phenylpropionyl)-3(*S*)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetylamino}butyl ester (108a) was prepared from **107a** by the method described for compound **57a** which afforded 156 mg (68%) of the title compound as a white solid. ^{1}H NMR (CD_3OD) δ 7.5-6.9 (17H, m), 5.16-5.02 (1H, dd), 4.88-4.71 (2H, m), 4.62-4.44 (2H, m), 4.42-4.28 (2H, m), 4.27-4.18 (1H, m), 3.47-3.41 (1H, m), 2.90-2.60 (5H, m), 2.46-2.4 (2H, m), 2.39-2.18 (2H, m).

4-(7-Methoxybenzoxazol-2-yl)-4-oxo-3(*S*)-{2-[2-oxo-5-(3-phenylpropionyl)-3(*S*)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid (108b) was prepared by the method

described for compound **69a** to give the title compound (50%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.41-6.88 (17H, m), 5.6-5.55 (0.5H, t), 5.48-5.43 (0.5H, t), 4.64-4.45 (2H, m), 4.45-4.30 (1H, m), 3.93 (1.5H, s), 3.90 (1.5H, s), 3.47-3.34 (1H, m), 3.10-2.85 (2H, m), 2.84-2.63 (5H, m), 2.6-2.4 (2H, m), 2.3-2.1 (2H, m).



t-Butyl (3*S*) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxo-pentanoate (123). Potassium fluoride (273mg, 4.70mmol) and then 2-chlorophenylmethyl thiol (373mg, 2.35mmol) were added to a stirred solution of (3*S*) t-butyl N-(allyloxycarbonyl)-3-amino-5-bromo-4-oxo-pentanoate (**122**; 749mg, 2.14mmol; WO 93 16710) in dimethylformamide (20ml). The mixture was stirred for 3.5h, quenched with water (50ml) and extracted with ethyl acetate (2 x 50ml). The combined organic extracts were washed with water (4 x 50ml) then brine

(50ml). They were dried ($MgSO_4$) and concentrated to afford an oil which was purified by flash chromatography (10-35% ethyl acetate/hexane) to afford 832 mg (91%) of a colourless solid: mp. 45-6 °C; $[\alpha]_D^{20}$ -19.0° (c 1.0, CH_2Cl_2); IR (film) 3340, 2980, 2935, 1725, 1712, 1511, 1503, 1474, 1446, 1421, 1393, 1368, 1281, 1244, 1157, 1052, 1040, 995, 764, 739; ^{1}H NMR ($CDCl_3$) δ 7.36 (2H, m), 7.21 (2H, m), 5.91 (2H, m), 5.27 (2H, m), 4.76 (1H, m), 4.59 (2H, d), 3.78 (2H, s), 3.36 (2H, m), 2.91 (1H, dd), 2.74 (1H, dd), 1.43 (9H, s). Anal. Calcd for $C_{20}H_{26}ClNO_5S$: C, 56.13; H, 6.12; N, 3.27; S, 7.49. Found: C, 56.08; H, 6.11; N, 3.26; S, 7.54. MS (C.I.) 430/28 (M^+ + 1, 3%), 374/2 (100).

t-Butyl (3*S*) 3(2(6-benzyl-1,2-dihydro-2-oxo-3(3-phenylpropionylamino)-1-pyridyl)acetylamino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124a). 6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-pyridyl acetic acid (**52b**; 300mg, 0.76mmol) in THF (7ml) was stirred with 1-hydroxybenzotriazole (205mg, 1.52mmol) and 1-(3-dimethylaminopropy-3-ethylcarbodiimide hydrochloride). After 3 min, water (12 drops) was added and the mixture stirred 10min then treated with t-butyl (3*S*) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (**123**) (325mg, 0.76mmol), bis (triphenylphosphine) palladium II chloride (20mg) and tributyltin hydride (0.6ml, 2.28mmol). The mixture was stirred for 5h at room temperature, poured into ethyl acetate and washed with aqueous 1M HCl (x2), aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and concentrated. The residue was triturated with pentane and the supernatant discarded. Chromatography (silica gel, 50% ethyl acetate/hexane)

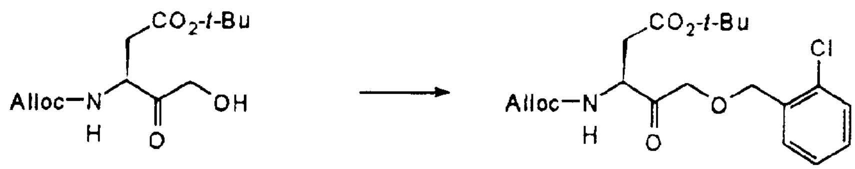
afforded a colourless foam (439mg, 81%): $[\alpha]_D^{21}$ -18.3 ° (c 0.5, CH_2Cl_2); IR (KBr) 3356, 3311, 1722, 1689, 1646, 1599, 1567, 1513, 1367, 1154; ^1H NMR ($CDCl_3$) δ 8.39 (1H, d), 8.23 (1H, s), 7.24 (14H, m), 6.16 (1H, d), 4.95 (1H, m), 4.63 (2H, m), 4.02 (2H, s), 3.74 (2H, s), 3.27 (2H, s), 2.85 (6H, m), 1.40 (9H, s). Anal. Calcd for $C_{39}H_{42}ClN_3O_6S$: C, 65.39; H, 5.91; N, 5.87. Found: C, 65.51; H, 5.99; N,5.77.

t-Butyl[3*S*(1*S*,9*S*)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124b) was prepared by a similar method as **124a** from the thioether **123** and 3*S*(1*S*,9*S*)-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (**45a**) to afford 452mg (50%) of colourless foam: mp 55-7 °C; $[\alpha]_D^{22}$ -94.0° (c 0.12, CH_2Cl_2); IR (KBr) 3288, 2934, 1741, 1722, 1686, 1666, 1644, 1523, 1433, 1260, 1225, 1146, 757; ^1H NMR ($CDCl_3$) δ 7.35 (3H, m), 7.20 (7H, m), 6.46 (1H, d), 5.21 (1H, m), 4.97 (2H, m), 4.56 (1H, m), 3.75 (2H, s), 3.25 (3H, m), 2.93 (5H, m), 2.71 (1H, dd), 2.55 (2H, m), 2.30 (1H, m), 1.92 (3H, m), 1.66 (2H, m), 1.42 (9H, s). Anal. Calcd for $C_{35}H_{43}ClN_4O_7S.0.25H_2O$: C, 59.73; H, 6.23; Cl, 5.04; N, 7.96; S, 4.56. Found: C, 59.73; H, 6.19; Cl, 5.10; N, 7.79; S, 4.58. MS (-FAB) 697 (M-1, 100).

(3*S*) 3(2(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetylamino-5-(2-chlorophenylmethylthio)-4-oxopentanoic acid (125a).

t-Butyl-3(2(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (**124a**) (400mg, 0.56mmol) in dichloromethane (3ml) at 0 °C was treated with trifluoroacetic acid (3ml) and stirred at 0 °C for 1h and room temperature for 0.5h. The solution was concentrated then redissolved in dichloromethane and reconcentrated. This procedure was repeated three times. The residue was stirred in ether for 1hr and filtered to yield a colourless solid (364mg, 99%): mp. 165-7 °C; $[\alpha]_D^{22}$ -27.7 ° (c 0.2, CH_2Cl_2); IR (KBr) 3289, 1712, 1682, 1657, 1645, 1593, 1562, 1527, 1497, 1416, 1203, 1182; ^{1}H NMR ($CDCl_3$) d 8.47 (1H, d), 8.21 (1H, s), 7.70 (1H, d), 7.22 (14H, m), 6.24 (1H, d), 5.03 (1H, m), 4.65 (2H, m), 4.06 (2H, s), 3.69 (2H, m), 3.23 (2H, m), 2.88 (6H, m).

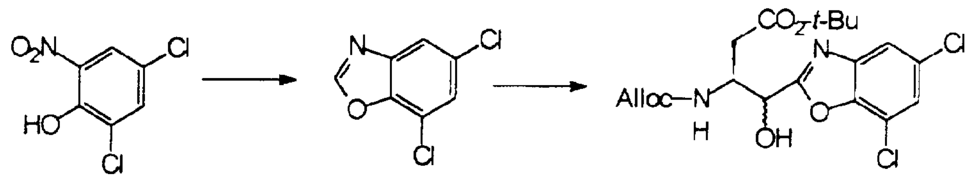
[3*S*(1*S*,9*S*)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionyl-amino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenyl-methylthio)-4-oxopentanoic acid (125b), was prepared by a similar method as **125a** from the t-butyl ester **124b** to afford 362mg (93%) of colourless powder: mp 76-80 °C; $[\alpha]_D^{21}$ -134 ° (c 0.10, MeOH); IR (KBr) 3309, 2935, 1725, 1658, 1528, 1445, 1417, 1277, 1219, 1175; ^{1}H NMR (D_6-DMSO) δ 8.80 (1H, d), 8.19 (1H, d 7.31 (9H, m), 5.09 (1H, m), 4.74 (1H, m), 4.63 (1H, m), 4.35 (1H, m), 3.76 (2H, m), 3.28 (3H, m), 2.80 (5H, m), 2.52 (4H, m), 2.16 (2H, m), 1.90 (3H, m). Anal. Calcd for $C_{31}H_{35}Cl_2N_4O_7S$. $0.25H_2O$: C, 57.49; H, 5.53; N, 8.65; S, 4.95. Found: C, 57.35; H, 5.43; N, 8.45; S, 4.88. MS (-FAB) 641 (M-1, 100).



81 **201**

2-Chlorophenylmethyliodide. A mixture of 2-chlorophenylmethylbromide (4g, 19.47mmol) and NaI (14g, 97.33mmol) in acetone (40ml) was stirred under reflux for 1 hour. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The residue was triturated with hexane and filtered. The solution was concentrated *in vacuo*, and the resulting oil purified by flash chromatography (silica, hexane) to afford the title compound (4.67g, 63%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.34 (4H, m), 4.54 (2H, s).

(3*S*) t-Butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethyloxy)-4-oxopentanoate (201). (3*S*) t-Butyl N-(allyloxycarbonyl)-3-amino-5-hydroxy-4-oxopentanoate (**81**, Chapman, et al., Bioorg. & Med. Chem. Lett., 2, pp. 613-618 (1992) 0.144g, 0.5mmol) and 2-chlorophenylmethyliodide (0.569g, 1.5mmol) in CH_2Cl_2 (4ml) were stirred vigorously with silver oxide (0.231g, 1mmol) and heated at 38 °C for 40 hours. The reaction mixture was cooled, filtered and the filtrate evaporated. The residue was purified by flash chromatography (silica, 0-20% ethylacetate in hexane) to afford the product as a colourless oil (0.138g, 67%): $[\alpha]_D^{24}$ +3.9 ° (c 1.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.37 (4H, m), 5.88 (2H, m), 5.26 (2H, m), 4.69 (2H, s), 4.57 (3H, m), 4.50 (1H, d), 4.35 (1H, d), 3.03 (1H, dd), 2.76 (1H, dd), 1.42 (9H, s).

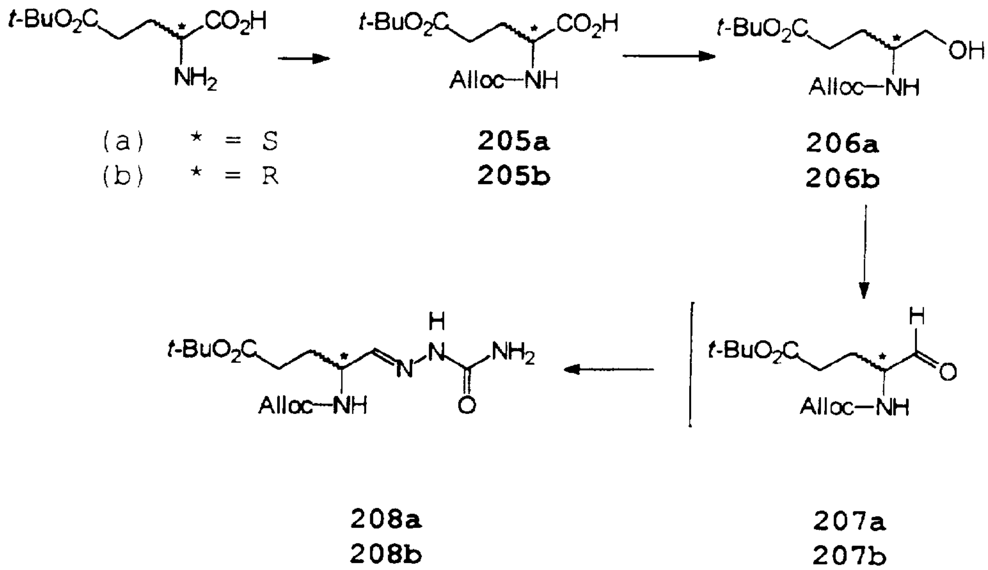


202 **203** **204**

5,7-Dichlorobenzoxazole (203). A solution of 2,4-dichloro-6-nitrophenol (**202**, 40g containing 20% moisture) in EtOAc (500ml) was dried using $MgSO_4$, filtered and the filter cake washed with a little EtOAc. Platinum on carbon (5% sulphided - 2g) was added and the mixture hydrogenated until uptake of H_2 ceased. Triethyl orthoformate (160ml) and p-toluene sulphonic acid (160mg) were added and the mixture refluxed for 4h. After cooling and removal of spent catalyst by filtration the solution was washed with sat. $NaHCO_3$ solution, water and brine, dried with $MgSO_4$ and evaporated to dryness. Trituration with hexane gave a solid which was collected by filtration, washed with hexane and dried to give the title compound (25.5g, 88%) as a crystalline solid: mp 98-99 °C; IR (KBr) 3119, 1610, 1590, 1510, 1452, 1393, 1296, 1067, 850; ^1H NMR ($CDCl_3$) δ 8.16 (1H, s), 7.69 (1H, d, J = 1.9), 7.42 (1H, d, J = 1.9); Anal. Calcd for $C_7H_3Cl_2NO$: C, 44.72; H, 1.61; N, 7.45; Cl, 37.70. Found: C, 44.84; H, 1.69; N, 7.31; Cl, 37.71.

(3*S*,4*RS*) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204). Magnesium bromide was prepared by reaction of Mg (7.45g, 0.30mole) in THF (516ml) with I_2 (50mg) and 1,2-dibromoethane (26.3ml, 57.3g, 0.30mole) at reflux for 2h and then cooling to -40 °C. To the above was

added rapidly via cannula a solution of 2-lithio-5,7-dichlorobenzoxazole at 70 °C (prepared from 5,7-dichlorobenzoxazole (**203**, 28.9g, 0.154mole) and butyl lithium (100ml 1.52M in hexane) in THF (150ml) at -70 °C). The mixture was stirred at -40 °C for 1h and then cooled to -70 °C before adding a solution of (3*S*) t-butyl N-(allyloxycarbonyl)-3-amino-4-oxo-butanoate (Chapman, et al., <u>Bioorg. & Med. Chem. Lett.</u>, 2, pp. 613-618 (1992)) (20.3g, 0.078mole) in THF (160ml) at less than -60 °C. The reaction was allowed to warm to ambient temperature and was stirred for 16h before quenching with ammonium chloride solution and extracting with 1:1 hexane:ethylacetate 600ml. The organic solution was washed with water and brine, dried with $MgSO_4$ and evaporated to a syrup (52.9g). Flash chromatography (SiO_2 250g -1l aliquots of 1:1 hexane: CH_2Cl_2 x2, CH_2Cl_2, 5% EtOAc in CH_2Cl_2, 10% EtOAc in CH_2Cl_2, 20% EtOAc in CH_2Cl_2) gave impure product 24.6g which on further chromatography (SiO_2 1:1 hexane:ether) give the title compound as a golden-brown glass (22.7g, 64%); IR (film) 3343, 2980, 1723, 1712, 1520, 1456, 1398, 1369, 1254, 1158, 993; ^{1}H NMR ($CDCl_3$) δ 7.60 (1H, m), 7.37 (1H, m), 5.72 (1H, m), 5.64 (0.5H, d), 5.10 (2.5H, m), 4.7-4.3 (4H, m), 2.9-2.6 (2H, m), 1.46 and 1.42 (9H combined, 2 x s). MS ES^+ Da/e 445 $(M + 1)^+$ Cl 35 62%, 447 $(M + 1)^+$ Cl 37 40%, 389 100%.



(a) * = S
(b) * = R

205a
205b

206a
206b

207a
207b

208a
208b

(2*S*)-N-Allyloxycarbonyl-5-(1,1-dimethylethyl)glutamate (205a). To a mixture of THF (200ml) and water (100ml) containing $NaHCO_3$ (16.6g, 0.2mol) was added glutaric acid t-butyl ester (10g, 49.2mmol) and then dropwise over 20 minutes allyl chloroformate (6.8ml, 64mmol). The mixture was stirred for 2 hours, extracted with EtOAc, washed with a sat. hydrogenocarbonate solution, water and a sat. salt solution, dried and evaporated to an oil **205a** (9.5g, 67.2%); $[\alpha]_D^{20}$ -6 ° (c 1.5, MeOH) ^{1}H NMR (D_6-DMSO) δ 6.10 (1H, d), 5.96-5.88 (1H, m), 5.31-5.12 (2H, m), 4.45 (2H, m), 3.90-3.84 (1H, t), 2.18 (2H, m), 1.85-1.76 (2H, m), 1.36 (9H, s).

(2*R*)-N-Allyloxycarbonyl-5-(1,1-dimethylethyl)glutamate (205b), was prepared by an analogous method to **205a** to afford a colourless oil (6.27g, 88%): $[\alpha]_D^{20}$ +16 ° (c 0.095, MeOH); IR (KBr) 3678, 3332, 3088, 2980, 2937, 1724, 1530, 1453, 1393, 1370, 1331, 1255, 1155, 1056, 995, 935, 845, 778, 757, 636, 583; ^{1}H NMR ($CDCl_3$) δ

9.24 (1H, broad s), 5.94-5.79 (1H, m), 5.58 (1H, d), 5.33-5.17 (2H, m), 4.55 (2H, d), 4.38-4.31 (1H, m), 2.41-1.95 (4H, m), 1.42 (9H, s); Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.4; H, 7.5; N, 4.8.

(4*S*) t-Butyl N-allyloxycarbonyl-4-amino-5-hydroxypentanoate (206a). To a solution of **205a** (3.6g, 12.5mmol) in THF (100ml) at 0 °C was added N-methyl morpholine (1.5ml, 13mmol) followed by isobutyl chloroformate, (1.1ml, 13mmol). After 15 minutes, this mixture was added to a suspension of $NaBH_4$ (0.95g, 25mmol) in THF (100ml) and MeOH (25ml) at -78 °C. After 2 hours at -70 °C, the mixture was quenched with acetic acid, diluted with EtOAc, washed with a sat. hydrogenocarbonate solution 3 times, water and a sat. solution of salt, dried and evaporated. Flash chromatography (2% MeOH in CH_2Cl_2) afforded **206a** as a colourless oil (2.4g, 70%): $[\alpha]_D^{20}$ -10 ° (c 3.88, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 5.84 (1H, m), 5.34-5.17 (3H, m), 4.56-4.53 (2H, m), 3.68-3.59 (2H, m), 2.98 (1H, m), 2.40-2.30 (2H, t), 1.84-1.78 (2H, m), 1.43 (9H, s); Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.1; H, 8.6; N, 6.0

(4*R*) t-Butyl N-allyloxycarbonyl-4-amino-5-hydroxypentanoate (206b), was prepared by an analogous method to **206a** which afforded the title compound as a light yellow oil (3.42g, 57%): $[\alpha]_D^{20}$ +14 (c 0.166, MeOH); IR (KBr) 3341, 3083, 2976, 2936, 2880, 1724, 1533, 1454, 1419, 1369, 1332, 1251, 1156, 1062, 997, 933, 846, 777, 647; ^1H NMR ($CDCl_3$) δ 5.98-5.81 (1H, m), 5.35-5.10 (3H, m), 4.55 (2H, d), 3.70-3.56 (3H, m),

2.50-2.47 (1H, broad s), 2.37-2.30 (2H, m), 1.89-1.74 (2H, m), 1.44 (9H, s); Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.9; H, 8.6; N, 5.6

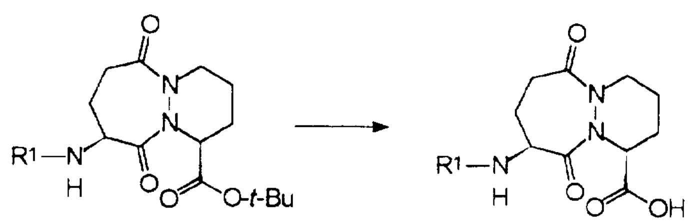
(4*S*) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate (207a). To a solution of DMSO (1.51g, 19.3mmol) in CH_2Cl_2 (25ml) at -70 °C was added oxalyl chloride (1.34g, 19.3mmol). After 10 minutes at -70 °C, a solution of **(206a)** (2.4g, 8.8mmol) in CH_2Cl_2 (10ml) was added dropwise and the mixture stirred for 15 minutes at -70 °C. Diisopropylethylamine (3.4g, 26.3mmol) was added and the mixture stirred at -25 °C for 15 minutes then diluting with EtOAc (50ml) washed with a solution of sodium hydrogen sulfate 2M, concentrated to give an oil which was used immediately without purification: ^{1}H NMR ($CDCl_3$) δ 9.5 (1H, s), 6.0-5.5 (2H, m), 5.5-5.1 (2H, m), 4.5 (2H, m), 4.2 (1H, m), 2.4-2.10 (2H, m), 2.05 (2H, m), 1.36 (9H, s).

(4*R*) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate (207b), was prepared by an analogous method to **207a** which afforded an oil (2.95g, 96%) which was used without further purification in the next step: $[\alpha]_D^{20}$ +21 ° (c 0.942, MeOH); ^{1}H NMR ($CDCl_3$) δ 9.58 (1H, s), 6.05-5.80 (1H, m), 5.57 (1H, broad s), 5.35-5.18 (2H, m), 4.56 (2H, d), 4.34-4.24 (1H, m), 2.38-2.16 (3H, m), 1.96-1.73 (1H, m), 1.43 (9H, s).

(4*S*) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate semicarbazone (208a). To a solution of **207a** (2.39g, 8.8mmol), in MeOH (20ml) was added sodium acetate (0.72g, 8.8mmol) and semicarbazide (0.98g, 8.8mmol)

stirred overnight, concentrated and diluted with CH_2Cl_2 (100ml), washed with water, dried and concentrated. Flash chromatography (2% MeOH in CH_2Cl_2) afforded **208a** (2.10g, 73%) as an oil: $[\alpha]_D^{20}$ -21 (c 2.55 °, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 9.98 (1H, s), 7.27 (1H, d), 5.8 (1H, m), 5.5 (1H, d), 5.35-5.19 (2H, m), 4.58 (2H, m), 4.14 (1H, m), 2.37 (2H, t), 2.09 (1H, m), 2.0-1.75 (2H, m); Anal. Calcd for $C_{14}H_{24}N_4O_5$: C, 51.21; H, 7.37; N, 17.06. Found: C, 50.2; H, 7.3; N, 16.1

(4*R*) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate semicarbazone (208b), was prepared by an analogous method to **208a** which afforded a glassy oil (2.37g, 66%): $[\alpha]_D^{20}$ +30 (c 0.26, $CHCl_3$); IR (KBr) 3476, 3360, 2979, 2923, 1700, 1586, 1527, 1427, 1394, 1369, 1338, 1253, 1156, 1060, 997, 929, 846, 775; ^1H NMR ($CDCl_3$) δ 9.87 (1H, s), 7.09 (1H, d), 6.05-5.75 (3H, m), 5.58 (1H, d), 5.32-5.16 (2H, m), 4.54 (2H, d), 4.35 (1H, m), 2.32-2.26 (2H, m), 2.15-1.55 (2H, m), 1.41 (9H, s); Anal. Calcd for $C_{14}H_{24}N_4O_5$: C, 51.21; H, 7.37; N, 17.06. Found: C, 51.0; H, 7.5; N, 16.7.



211	(b) R^1 = $MeSO_2$	**212**	(b) R^1 = $MeSO_2$
	(c) R^1 = MeCO		(c) R^1 = MeCO
	(d) R^1 = $PhCH_2OCO$		(d) R^1 = $PhCH_2OCO$
	(e) R^1 = PhCO		(e) R^1 = PhCO
	(f) R^1 = Fmoc		(f) R^1 = Fmoc

(1*S*,9*S*) t-Butyl 6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (211b). A solution of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 831mg, 2.79mmol) and diisopropylethylamine (1.22ml, 6.99mmol, 2.5 equiv) in CH_2Cl_2 (10ml) under dry nitrogen was treated with methanesulphonyl chloride (237µl, 3.07mmol 1.1 equiv). The mixture was stirred for 1h, diluted with EtOAc (75ml) and washed with saturated $NaHCO_3$ (50ml) and saturated aqueous sodium chloride (30ml), dried ($MgSO_4$) and concentrated. Flash chromatography (10-35% EtOAc in CH_2Cl_2) afforded **211b** (806mg, 77%) as a colourless solid: mp 68-70 °C; $[\alpha]_D^{23}$ -109 (c 1.09, CH_2Cl_2); IR (KBr) 3270, 2980, 2939, 1735, 1677, 1458, 1447, 1418, 1396, 1370, 1328, 1272, 1252, 1232, 1222, 1156, 1131, 991; ^1H NMR ($CDCl_3$) δ 6.15 (1H, d), 5.31 (1H, m), 4.65-4.11 (2H, m), 3.47 (1H, m) 2.99 (3H, s), 2.89 (1H, m), 2.72-2.51 (2H, m), 2.34 (1H, m), 2.26 (1H, m), 2.05-1.62 (4H, m), 1.47 (9H, s); Anal. Calcd for $C_{15}H_{23}N_3O_6S$: C, 47.97; H, 6.71; N, 11.19; S, 8.54. Found: C, 48.28; H, 6.68; N, 10.86; S, 8.28. MS (+ FAB) 376 (M^+ + 1, 66%), 320 (100).

(1*S*,9*S*) t-Butyl 9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a]-[1,2]diazepine-1-carboxylate (211c). Acetic anhydride (307mg, 3.01mmol) was added to a stirred mixture of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 813.7mg, 2.74mmol), diisopropylethylamine (884mg, 6.84mmol) and CH_2Cl_2

(20ml). The mixture was kept for 1h then diluted with EtOAc, washed with $NaHCO_3$ solution then brine, dried ($MgSO_4$) and concentrated to yield a colourless oil. The product was purified by flash chromatography (0.5-8% $MeOH/CH_2Cl_2$) to afford **211c** (804mg, 71%) of colourless powder: mp 162-3 °C; $[\alpha]_D^{23}$ -109 (c 1.03, CH_2Cl_2); IR(KBr) 3358, 2974, 1733, 1693, 1668, 1528, 1462, 1431, 1406, 1371, 1278, 1271, 1250, 1233, 1217, 1154, 1124; δ ^1H NMR ($CDCl_3$) d 6.32 (1H, d), 5.29-5.25 (1H, m), 4.98-4.85 (1H, m), 4.68-4.58 (1H, m), 3.55-3.39 (1H, m), 2.91-2.66 (2H, m), 2.39-2.18 (2H, m), 2.03 (3H, s), 1.88-1.64 (4H, m), 1.47 (9H, s); Anal. Calcd for $C_{16}H_{25}N_3O_5$: C, 56.62; H, 7.43; N, 12.38. Found: C, 56.62; H, 7.43; N,12.36; MS (+ FAB) 340 (M^+ + 1, 40%), 284 (100).

(1*S*,9*S*) t-Butyl 9-(benzyloxycarbonylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (211d). Benzyl chloroformate (1.07g) was added dropwise to a stirred ice cold mixture of the (1*S*,9*S*) t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 1.55g, 5.21mmol), $NaHCO_3$ (0.66g, 7.82mmol), dioxan (32ml) and water (8ml). The mixture was kept at 5 °C for 15min then for 2h at room temperature. The mixture was diluted with EtOAc (50ml), washed twice with sat. $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated. The oily residue was purified by flash chromatography to afford **211d** (1.98g, 88%) of a colourless oil: $[\alpha]_D^{24}$ -56.4 (c 1.0, CH_2Cl_2); IR(thin film) 3325, 2979, 2946, 1728, 1677, 1528, 1456, 1422, 1370, 1340, 1272, 1245, 1156, 1122, 1056, 916, 734, 699; ^1H NMR ($CDCl_3$) δ 7.29

(5H, m), 5.81-5.72 (1H, m), 5.26-5.20 (1H, m), 5.05 (2H, s), 4.69-4.51 (2H, m), 3.48-3.36 (1H, m), 2.81-2.51 (2H, m), 2.34-2.19 (2H, m), 1.90-1.54 (4H, m), 1.41 (9H, s); Anal. Calcd for $C_{22}H_{29}N_3O_6{\bullet}H_2O$: C, 58.79; H, 6.92; N, 9.35. Found: C, 59.10; H, 6.57; N, 9.25; MS (ES +) 454 (M^++Na, 87%), 432 (M^++1, 100).

(1*S*,9*S*) t-Butyl 9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylate (211e). A solution of benzoyl chloride (1.61g, 11.47mmol) in CH_2Cl_2 (15ml) was added dropwise to a stirred ice cold mixture of (1*S*,9*S*) t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 3.1g, 10.43mmol), dry CH_2Cl_2 (20ml) and diisopropylethylamine (4.54ml, 26.06mmol). The mixture was kept cold for 1h then left at room temperature for 0.5h. The mixture was diluted with CH_2Cl_2, washed twice with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-5% methanol in CH_2Cl_2) to afford **211e** (4.0g, 96%) of a colourless glass: mp 74-76 °C; $[\alpha]_D^{30}$ -75.0 ° (c 0.12, CH_2Cl_2). IR (KBr) 3350, 2979, 2938, 1736, 1677, 1662, 1536, 1422, 1276, 1250, 1155; ^{1}H NMR ($CDCl_3$) δ 8.72 (2H, m), 7.53-7.40 (3H, m), 7.07 (1H, d, *J* = 7.2), 5.30 (1H, dd, *J* = 3.0, 5.8), 5.12 (1H, m), 4.66 (1H, m), 3.51 (1H, m), 2.90 (2H, m), 2.38 (1H, dd, *J* 13.2, 6.8), 2.25 (1H, m), 1.9 (2H, m), 1.70 (1H, m). Anal. Calcd for $C_{21}H_{27}N_3O_5$ $0.5H_2O$: C, 61.45; H, 6.88; N, 10.24. Found C, 61.69; H, 6.71; N, 10.18.

(1*S*,9*S*) t-Butyl 6,10-dioxo-9-(fluoren-9-ylmethyloxy-carbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-

pyridazino[1,2-a][1,2]-diazepine-1-carboxylate (211f), was prepared in a similar manner to **211e**, except 9-fluorenylmethylchloroformate was used instead of benzoylchloride to give a white glassy solid **211f** (2.14g, 89%): mp 190-192 °C; $[\alpha]_D^{25}$ -81.5 ° (c 0.1, CH_2Cl_2). IR (KBr) 3335, 2977, 1731, 1678, 1450, 1421, 1246, 1156, 742; ^1H NMR ($CDCl_3$) δ 7.60 (2H, m), 7.57 (2H, m), 7.50-7.26 (4H, m), 5.60 (1H, d, J = 7.8), 5.28 (1H, m), 4.67 (2H, m), 4.38 (2H, m), 4.23 (1H, m), 3.59-3.41 (1H, m), 2.92-2.65 (2H, m), 2.41-2.21 (2H, m), 1.95-1.58 (4H, m), 1.47 (9H, s). MS(ES^-, m/z) 520 (M^+ + 1, 97%), 179 (100%).

(1*S*,9*S*) 6,10-Dioxo-9-methysulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylic acid (212b), was synthesized by the same method as compound **212e** (635mg, 85%) as a colourless powder: mp 209-12 °C; $[a]_D^{24}$ -132 (c 0.12, MeOH); IR (KBr) 3308, 2940, 1717, 1707, 1699, 1619, 1469, 1456, 1442, 1417, 1391, 1348, 1339, 1330, 1310, 1271, 1247, 1222, 1175, 1152, 1133, 993, 976; ^1H NMR (CD_3OD) δ 5.35 (1H, m), 4.58-4.48 (1H, m), 4.46-4.36 (1H, m), 3.60-3.42 (1H, m), 3.01-2.87 (1H, m), 2.95 (3H, s), 2.55-2.39 (1H, m), 2.32-2.20 (2H, m), 2.09-1.89 (2H, m), 1.78-1.62 (2H, m); Anal. Calcd for $C_{11}H_{17}N_3O_6S$: C, 41.37; H, 5.37; N, 13.16; S, 10.04. Found: C, 41.59; H, 5.32; N, 12.75; S, 9.76; MS(ES -). Accurate Mass calculated for $C11H_{18}N_3O_6S$ (MH^+): 320.0916. Found: 320.0943.

(1*S*,9*S*) 9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (212c), was prepared from **211e** the same

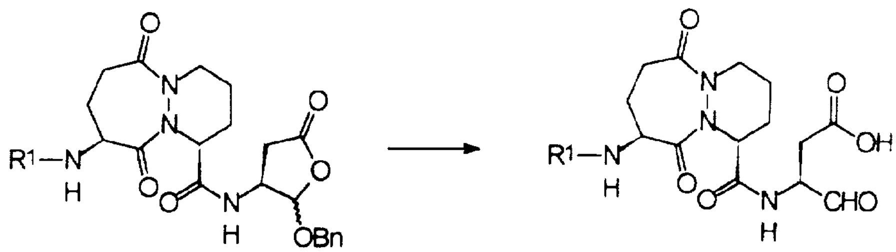
method as compound **212e** as a white glassy solid (595mg, 77%): mp >250 °C; $[\alpha]_D^{24}$ -153 (c 0.10, MeOH); IR (KBr) 3280, 2942, 1742, 1697, 1675, 1650, 1616, 1548, 1470, 1443, 1281, 1249, 1202, 1187, 1171; ^1H NMR (CD_3OD) δ 5.35-5.31 (1H, m), 4.81-4.71 (1H, m), 4.61-4.46 (1H, m), 3.59-3.44 (2H, m), 3.11-2.94 (1H, m), 2.58-2.39 (1H, m), 2.36-2.19 (2H, m), 2.11-1.83 (3H, m), 1.99 (3H, s), 1.78-1.56 (2H, m); Anal. Calcd for $C_{12}H_{17}N_3O_5$: C, 50.88; H, 6.05; N, 14.83. Found: C, 50.82; H, 6.02; N, 14.58; MS (ES -) 282 (M-1, 100%): Accurate Mass calculated for $C_{12}H_{18}N_3O_5$ (MH^+): 284.1246. Found: 284.1258.

(1*S*,9*S*) 9-Benzyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylic acid (212d), was prepared from **211d** by the same method as compound **212e** as colourless crystals (170mg, 97%): mp 60-100 °C; $[\alpha]_D^{22}$ -103 (c 0.10, MeOH); IR (KBr) 3341, 2947, 1728, 1675, 1531, 1456, 1422, 1339, 1272, 1248, 1221, 1174, 1122, 1056, 982, 699; ^1H NMR ($CDCl_3$) δ 7.35 (5H, s), 5.65 (1H, d), 5.48-5.40 (1H, m), 5.10 (2H, s), 4.76-4.57 (2H, m), 3.49-3.30 (2H, m), 2.92-2.59 (2H, m), 2.40-2.27 (2H, m), 1.97-1.67 (4H, m); MS (ES -) 374 (M - 1, 100%). Accurate mass calculated for $C_{18}H_{22}N_3O_6$ (MH^+): 376.1509. Found: 376.1483. Accurate mass calculated for $C_{18}H_{21}N_3O_6Na$ (MNa^+): 398.1328. Found: 398.1315.

(1*S*,9*S*) 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylic acid (212e). TFA (20ml) was added to an ice cold stirred solution of the t-butyl ester **211e** (4.15g,

10.34mmol) in dry CH_2Cl_2 (20ml). The mixture was kept cold for 1.5h then left for 2.5h at rt, concentrated. TFA was removed by repeated concentrations of CH_2Cl_2\ether and ether solutions of the residue. Finally trituration of the residue with ether afforded **212e** 3.05g (85%) of a white glassy solid: mp 118-126 °C; $[\alpha]_D^{24}$ -70.5 ° (c 0.1, CH_2Cl_2). IR (KBr) 3361, 2943, 1737, 1659, 1537, 1426, 1220, 1174; ^{1}H NMR ($CDCl_3$) δ 7.80 (2H, m), 7.54-7.33 (4H, m), 8.83 (brs), 5.44 (1H, m), 5.26-5.13 (1H, m), 4.66 (1H, m), 3.59-3.41 (1H, m), 2.97, 2.76 (2H, 2m), 2.36 (2H, m), 1.98 (2H, m), 1.75 (2H, m). MS(ES^-, m/z) 344 (M - 1, 100%).

(1*S*,9*S*) 6,10-Dioxo-9(fluoren-9-ylmethyloxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylic acid (212f), was prepared from **211f** in 96% yield by the same method as for **212e**: mp 120-126 °C; $[\alpha]_D^{25}$ -72.5 ° (c 0.1, CH_2Cl_2). IR (KBr) 3406, 2950, 1725, 1670, 1526, 1449, 1421, 1272, 1248, 1223, 1175, 761, 741; ^{1}H NMR ($CDCl_3$) δ 7.76 (2H, m), 7.62-7.26 (4H, m), 6.07, 5.76 (2H, brs, d, d, *J* = 2.9), 5.46, 5.36 (1H, 2m), 4.79-4.54 (2H, m), 4.77 (2H, m), 4.21 (1H, m), 3.41 (1H, m), 2.89 (1H, m), 2.69 (1H, m), 2.35 (2H, m), 1.98, 1.73 (4H, 2m). MS(ES^-, m/z) 462 (M^+ - 1, 50%), 240 (100%).



(213) (c) R^1 = MeCO
(e) R^1 = PhCO

(214) (c) R^1 = MeCO
(e) R^1 = PhCO

[2*RS*,3*S*(1*S*,9*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-9-(acetylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213c), was synthesized from **212c** by the same method as compound **213e** to afford a mixture of diastereomers (193mg, 36%) as colourless crystals: IR (KBr) 3272, 1799, 1701, 1682, 1650, 1555, 1424, 1412, 1278, 1258, 1221, 1122, 937; ^{1}H NMR ($CDCl_3$) δ 7.41-7.28 (5H, m), 6.52 (0.5H, d), 6.38 (0.5H, d), 6.22 (0.5H, d), 5.57 (0.5H, d), 5.36 (0.5H, s) 5.10-5.05 (1H, m), 5.00-4.45 (5.5H, m), 3.19-2.84 (3H, m), 2.72-2.56 (1H, m), 2.51-2.25 (2H, m), 2.02 (3H, s), 1.98-1.70 (3H, m), 1.66-1.56 (3H, m); Anal. Calcd for $C_{23}H_{28}N_4O_7$: C, 58.47; H, 5.97; N, 11.86. Found: C, 58.37; H, 6.09; N, 11.47. MS (ES -) 471 (M-1, 100%). Accurate mass calculated for $C_{23}H_{29}N_4O_7$ (MH^+): 473.2036. Found: 473.2012. Accurate mass calculated for $C_{23}H_{28}N_4O_7Na$ (Mna^+): 495.1856. Found: 495.1853.

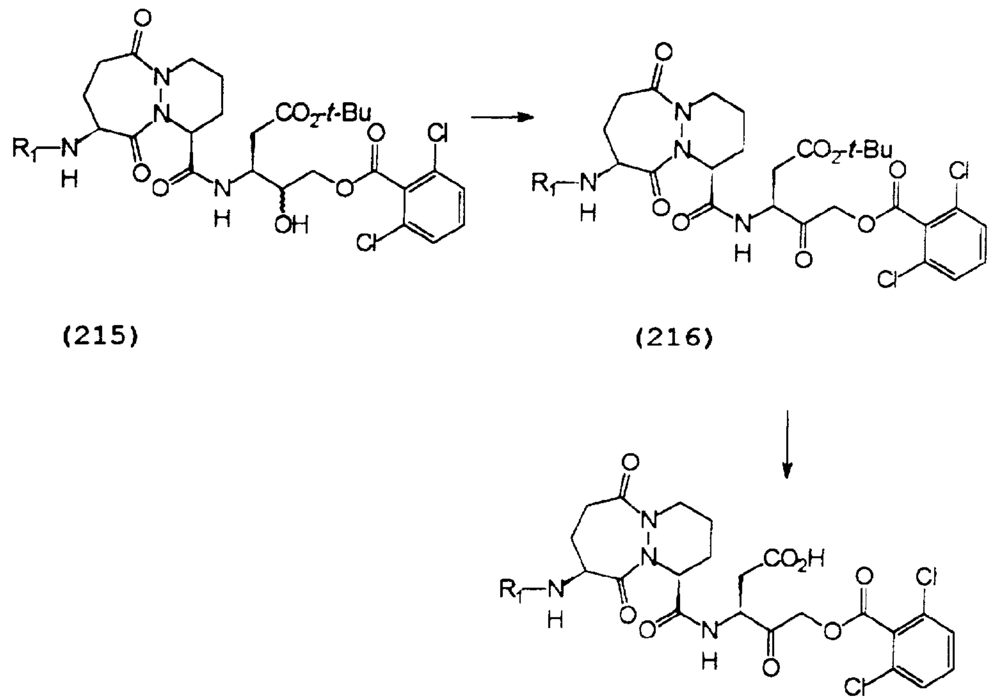
[1*S*,9S(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamide (213e). Tributyltin hydride (2.2ml, 8.18mmol) was added dropwise to a solution of

acid **212e** (1.95g, 5.6mmol), (3*S*, 2*RS*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett., 2, pp. 615-618 (1992); 1.80g, 6.16mmol) and $(Ph_3P)_2PdCl_2$ (50mg) in dry CH_2Cl_2 (36ml), with stirring, under dry nitrogen. After 5 min 1-hydroxybenzotriazole (1.51g, 11.2mmol 6.72mmol) was added followed after cooling (ice/H_2O) by ethyldimethylaminopropyl carbodiimide hydrochloride (1.29g, 6.72mmol). After 5 mins the cooling bath was removed and the mixture was kept at room temperature for 4h, diluted with EtOAc, washed with 1M HCl, brine, sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Flash chromatography (silica gel, 0-90% EtOAc in CH_2Cl_2) gave the product as a white solid (2.34g, 78%): IR (KBr) 3499, 1792, 1658, 1536, 1421, 1279, 1257, 1123, 977, 699; ^{1}H NMR ($CDCl_3$) δ 7.81 (2H, m), 7.54-7.34 (8H, m), 7.1, 6.97, 6.89, 6.48 (2H, m, d, *J* 7.7, d, *J* = 7.5, d, *J* = 7.6), 5.57, 5.28 (1H, d, *J* = 5.2, s), 5.23-5.07 (2H, m), 4.93-4.42, 3.22-2.70, 2.51-2.26, 2.08-1.69, 1.22 (15H, 5m). Anal. Calcd for $C_{28}H_{30}N_4O_7$ $0.5H_2O$: C, 61.87; H, 5.75; N, 10.32. Found C, 62.02; H, 5.65; N, 10.25.

[3*S*(1*S*,9*S*)] 3-(9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214c), was synthesized from **213c** by a method similar to the method used to synthesize **214e** from **213e** to provide colourless crystals (140mg, 99%): mp 90-180 °C; $[\alpha]_D^{22}$ -114 (c 0.10, MeOH); IR (KBr) 3334, 3070, 2946, 1787, 1658, 1543, 1422, 1277, 1258; ^{1}H NMR (d^6-DMSO) δ 8.66 (1H, m), 8.18 (1H, d), 6.76 (1H, s), 5.08 (1H, m), 4.68 (1H, m), 4.30 (1H, m), 2.92-2.70 (2H, m),

2.27-2.06 (3H, m), 1.95-1.72 (4H, m), 1.85 (3H, s), 1.58 (2H, m); MS(ES -) 381 (M-1, 100%); Accurate mass calculated for $C_{16}H_{23}N_4O_7$ (MH^+): 383.1567. Found: 383.1548.

[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4-oxobutanoic acid (214e). A mixture of **213e** (2.29g, 4.28mmol), 10% palladium on carbon (1.8g) and MeOH (160ml) was stirred under H_2 at atmospheric pressure for 6.3h. After filtering and concentrating the hydrogenation was repeated with fresh catalyst (1.8g) for 5h. After filtering and concentrating the residue was triturated with diethyl ether, filtered and washed well with ether to give **214e** as a white solid (1.67g, 88%): mp 143-147 °C; $[\alpha a]_D^{23}$ -125 ° (c 0.2, CH_3OH). IR (KBr) 3391, 1657, 1651, 1538, 1421, 1280, 1258; ^{1}H NMR (CD_3OD) δ 7.90 (2H, m), 7.63-7.46 (3H, m), 5.25 (1H, m), 5.08-4.85 (1H, m), 4.68-4.53 (2H, m), 4.33-4.24 (1H, m), 3.62-3.44, 3.22-3.11, 2.75-2.21, 2.15-1.92, 1.73-1.66 (11H, 5m). Anal. Calcd for $C_{21}H_{24}N_4O_7$ H_2O: C, 54.54; H, 5.67; N, 12.11. Found C, 54.48; H, 5.63; N, 11.92.



(215) (216)

(217)

(c) R_1 = MeCO
(d) R_1 = $PhCH_2OCO$
(e) R_1 = PhCO

[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-[9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-hydroxypentanoate (215c), was synthesized from **214c** by the same method as compound **215e**, to afford a mixture of diastereomers as a white glassy solid (398mg, 84%): IR (KBr) 3338, 2977, 1738, 1658, 1562, 1541, 1433, 1368, 1277, 1150; ^{1}H NMR ($CDCl_3$) δ 7.36-7.32 (3H, m), 6.91 (1H, d), 6.30 (1H, d), 5.15-5.09 (1H, m) 5.01-4.88 (1H, m), 4.61-4.44 (2H, m), 4.37-4.08 (3H, m), 3.32-3.18 (1H, m), 3.04-2.89 (1H, m), 2.82-2.51 (4H, m), 2.39-2.29 (1H, m), 2.08-1.64 (4H, m) 2.02 (3H, s); Anal. Calcd for

$C_{28}H_{34}N_4Cl_2O_9$: C, 52.26; H, 5.64; N, 8.71. Found: C, 52.44; H, 5.87; N, 8.16. MS (ES -) 645/3/1 (M-1, 26%), 189 (81), 134 (100). Accurate mass calculated for $C_{28}H_{37}N_4Cl_2O_9$ (MH^+): 643.1938. Found: 643.1924. Accurate mass calculated for $C_{28}H_{36}N_4Cl_2O_9Na$ (MNa^+) 665.1757. Found: 665.1756.

[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzyloxy)-4-hydroxypentanoate (215d), was synthesized from **214d** by the same method as compound **215e** to afford a mixture of diastereomers (657mg, 70%) as a glassy white solid: IR (KBr) 3420, 3361, 2975, 2931, 1716, 1658, 1529, 1434, 1367, 1348, 1250, 1157, 1083, 1055; ^1H NMR ($CDCl_3$) δ 7.32 (8H, m), 7.14 (1H, d), 5.81 (1H, d), 5.15 (1H, m), 5.07 (2H, s), 4.74-4.65 (1H, m), 4.58-4.22 (4H, m), 4.15-4.06 (1H, m), 3.72 (1H, m), 3.32-3.21 (1H, m), 3.04-2.94 (1H, m), 2.69-2.52 (3H, m), 2.33-2.27 (1H, m), 1.95-1.59 (4H, m), 1.28 (9H, s); Anal. Calcd for $C_{34}H_{40}N_4Cl_2O_{10}.0.5\ H_2O$: C, 54.70; H, 5.54; N, 7.50. Found: C, 54.98; H, 5.59; N, 7.24. MS (ES -) 737/5/3 (M-1, 22%), 193/1/89 (100). Accurate mass calculated for $C_{34}H_{41}N_4Cl_2O_{10}$ (MH^+) 735.2120. Found: 735.2181.

[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzyloxy)-4-hydroxypentanoate (215e), Tributyltin hydride (4.6ml; 11.4mmol) was added dropwise to a stirred mixture of (3*S*,4*RS*) t-Butyl (N-allyloxycarbonyl)-3-amino-5-(2,6-dichlorobenzoyloxy)-4-

hydroxypentanoate (prepared by a method similar to the method described in Revesz et al., Tetrahedron. Lett., 35, pp. 9693-9696 (1994)) (2.64g; 5.7mmol), $(Ph_3P)_2PdCl_2$ (50mg), CH_2Cl_2 (100ml) and DMF (20ml) at room temperature. The mixture was stirred for a further 10min was then 1-hydroxybenzotriazole (1.54g, 11.4mmol)was added. The mixture was cooled to 0 ^{0}C then ethyldimethylaminopropyl carbodiimide hydrochloride (1.31g; 6.84mmol) added. The mixture was kept at this temperature for 15min then at room temperature for 17h. The mixture was diluted with EtOAc (300ml), washed with 1M HCl (2x100ml), sat. aq. $NaHCO_3$ (3x100ml) and brine (2x100ml), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (2-5% ($MeOH/CH_2Cl_2$) to afford 3.24g (81%) of **215e** as a glassy solid: mp 106-110 °C; IR (KBr) 3354, 1737, 1659, 1531, 1433, 1276, 1150; ^{1}H NMR ($CDCl_3$) δ 7.80 (2H, dd, J = 7.9 and 1.5), 7.75-7.26 (6H, m), 7.14-6.76 (2H, m), 5.30-5.02 (2H, m), 4.63-4.11 (5H, m), 3.44-3.26 (2H, m), 3.10-2.30 (5H, m), 2.10-1.60 (5H, m), 1.44 (9H, s); Anal. Calcd for $C_{33}H_{38}Cl_2N_4O_9$. $0.75H_2O$: C, 55.12; H, 5.54; N, 7.79; Cl, 9.86. Found: C, 55.04; H, 5.34; N, 7.80; Cl, 10.24. MS (ES +) 709/7/5 (M + 1), 378 (59), 324 (64), 322 (100).

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (216c), was synthesized from **215c** by the same method as compound **216e** as a glassy white solid (300mg, 83%): mp 80-125 °C; $[\alpha]_D^{23}$ -89.1 (c 1.08, CH_2Cl_2); IR (KBr) 3356, 2979, 2935, 1740, 1659, 1532,

1434, 1369, 1276, 1260, 1151; ^{1}H NMR ($CDCl_3$) δ 7.39-7.32 (3H, m), 7.13 (1H, d), 6.34 (1H, d), 5.22-5.17 (1H, m), 5.11 (1H, d), 5.04 (1H, d), 4.99-4.88 (2H, m), 4.64-4.52 (1H, m), 3.29-3.11 (1H, m), 3.05-2.67 (4H, m), 2.39-2.29 (1H, m), 2.02 (3H, s), 1.98-1.75 (4H, m), 1.46 (9H, s); Anal. Calcd for $C_{28}H_{34}N_4Cl_2O_9$: C, 52.42; H, 5.34; N, 8.73. Found: C, 52.53; H, 5.70; N, 7.85. MS (ES -) 643/41/39 (M-1, 100%). Accurate mass calculated for $C_{28}H_{35}N_4Cl_2O_9$ (MH^+): 641.1781. Found: 641.1735. Accurate mass calculated for $C_{28}H_{34}N_4Cl_2O_9Na$ (Mna^+): 663.1601. Found: 663.1542.

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-benzyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (216d), was synthesized from **215d** by the same method as compound **216e** to afford **216d** as a white glassy solid (688mg, 68%): mp 90-170 °C; $[\alpha]_D^{25}$ -83.4 (c 1.01, CH_2Cl_2); IR (KBr) 3338, 2933, 1736, 1670, 1525, 1433, 1417, 1368, 1258, 1151, 1056, 1031; ^{1}H NMR ($CDCl_3$) δ 7.33 (8H, m), 7.18 (1H, d), 5.65 (1H, d), 5.19 (1H, m), 5.09 (2H, s), 4.98-4.86 (1H, m), 4.82-4.49 (2H, d), 3.30-3.07 (1H, m), 3.05-2.59 (4H, m), 2.42-2.27 (1H, m), 2.18-1.59 (5H, m), 1.42 (9H, s); MS (ES-) 737/5/3 (M, 13%), 185 (100).

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (216e). Dess-Martin reagent (3.82g; 9.0mmol) was added to a stirred solution of the alcohol **215e** (3.17g; 4.5mmol) in

CH_2Cl_2 (100ml). The mixture was sirred for 1h, diluted with EtOAc (300ml), then washed with a 1:1 mixture of sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ (100ml) followed by brine (100ml). The mixture was dried ($MgSO_4$) then concentrated. The residue was purified by flash chromatography to afford 2.2g (70%) of **216e** as a colourless solid: mp 102-107 °C; $[\alpha]_D^{32}$ -82.5 (c 0.1, CH_2Cl_2); IR (KBr) 3374, 2937, 1739, 1661, 1525, 1433, 1275, 1260, 1152; ^1H NMR ($CDCl_3$) δ 7.85-7.78 (2H, m), 7.57-7.32 (6H, m), 7.09 (1H, d, *J* = 7.9), 7.01 (1H, d, *J* 7.3), 5.25-5.16 (1H, m), 5.16-5.05 (1H, m), 5.15 (1H, d), 5.03 (1H, d), 4.99-4.90 (1H, m), 4.68-4.54 (1H, m), 3.31-3.17 (1H, m), 3.17-2.72 (4H, m), 2.45-2.35 (1H, m), 2.30-1.66 (5H, m), 1.44 (9H, s); Anal. Calcd for $C_{33}H_{36}Cl_2N_4O_9$. $0.5H_2O$: C, 55.62; H, 5.23; N, 7.86; Cl, 9.95. Found: C, 55.79; H, 5.15; N, 7.80; Cl 9.81. MS (ES +) 729/7/5 (M + Na), 707/5/3 (M + 1), 163 (100%).

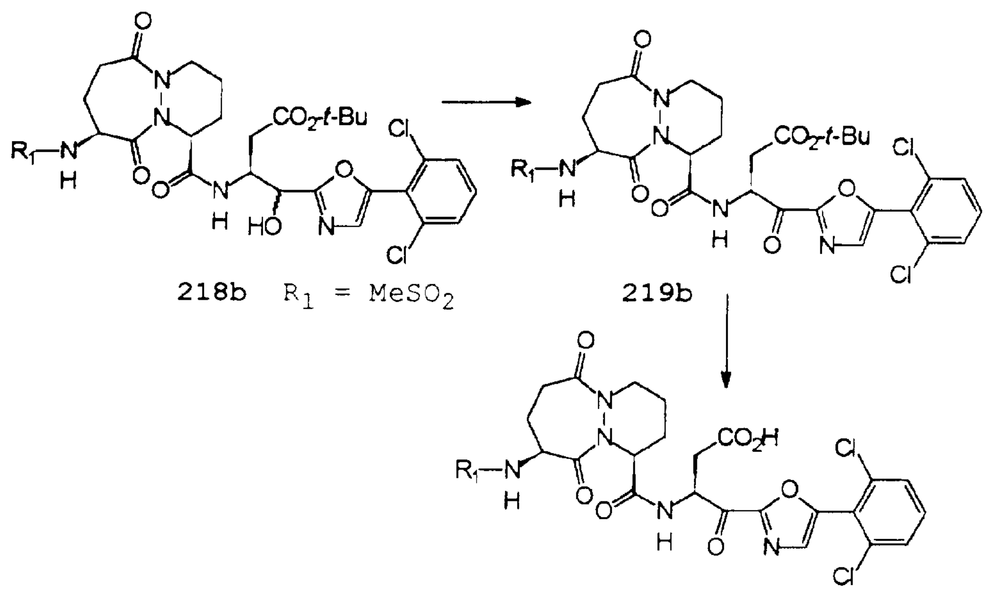
[3*S*(1*S*,9*S*)] 3-(9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (217c), was synthesized from **216c** by the same method as compound **217e** as a glassy white solid (166mg, 66%): mp 85-175 °C; $[\alpha]_D^{25}$ -156 (c 0.13, MeOH); IR (KBr) 3373, 2929, 1742, 1659, 1562, 1533, 1433, 1412, 1274, 1266, 1223, 1197, 1145, 1138; ^1H NMR (CD_3OD) δ 7.38 (3H, s), 5.14-5.03 (1H, m), 4.49-4.32 (2H, m), 3.50-3.27 (1H, m), 3.11-2.92 (1H, m), 2.84-2.62 (2H, m), 2.46-2.11 (2H, m), 2.05-1.46 (5H, m), 1.92 (3H, s); Anal. Calcd for $C_{24}H_{26}N_4Cl_2O_9.H_2O$: C, 47.77; H, 4.68; N, 9.29. Found: C, 47.75; N, 4.59; N, 9.07. MS (ES +) 627/5/3 (M+K, 21%), 611/9/7 (M+Na, 87), 589/7/5 (M^+ +1, 71),

266 (100); Accurate mass calculated for $C_{24}H_{27}N_4Cl_2O_9$ (MH^+): 585.1155. Found: 585.1134.

[3*S*(1*S*,9*S*)] 3-(9-Benzyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (217d), was synthesized from **216d** by the same method as compound **217e** to afford **217d** as a white glassy solid (310mg, 96%): mp 85-110 °C; $[\alpha]_D^{24}$ -85.9 (c 0.13, MeOH); IR (KBr) 3351, 2945, 1738, 1669, 1524, 1433, 1258, 1147, 1057; ^{1}H NMR (CD_3OD) δ 7.56 (4H, m), 7.45 (5H, m), 5.32 (2H, m), 5.20 (2H, s), 4.76-4.48 (3H, m), 3.65-3.38 (3H, m), 3.27-3.09 (2H, m), 3.03-2.89 (2H, m), 2.65-2.24 (3H, m), 2.19-1.62 (5H, m); MS (ES -) 679/7/5 (M-1, 100%); Accurate mass calculated for $C_{30}H_{31}N_4Cl_2O_{10}$ (MH^+): 677.1417. Found: 677.1430.

[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (217e), TFA (25ml) was added dropwise to an ice cold stirred solution of the ester **216e** (2.11g, 3.0mmol). The mixture was stirred at 0 °C for 20min then at room temperature for 1h. The mixture was evaporated to dryness then coevaporated with ether three times. Addition of dry ether (50 ml) and filtration afforded 1.9g (98%) of **217e** as a colourless solid: mp 126-130 °C; $[\alpha]_D^{30}$ -122.0 (c 0.1, MeOH); IR (KBr) 3322, 1740, 1658, 1651, 1532, 1433, 1277, 1150; ^{1}H NMR (D_6-DMSO) δ 8.87 (1H, d, *J* = 7.4), 8.61 (1H, d, *J* = 7.8), 7.92-7.86 (2H, m), 7.65-7.43 (6H, m), 5.25-5.12 (3H, m), 4.94-4.60 (2H, m), 4.44-4.22 (1H, m),

3.43-3.10 (1H, m), 3.00-2.52 (3H, m), 2.45-2.10 (3H, m), 2.10-1.75 (2H, m), 1.75-1.50 (2H, m); Anal. Calcd for $C_{29}H_{28}Cl_2N_4O_9 \cdot 1H_2O$: C, 52.34; H, 4.54; N, 8.42; Cl, 10.66. Found: C, 52.02; H, 4.36; N, 8.12; Cl, 10.36. MS (ES -) 649/7/5 (M - 1), 411 (100%).



218b R_1 = $MeSO_2$ **219b** **220b**

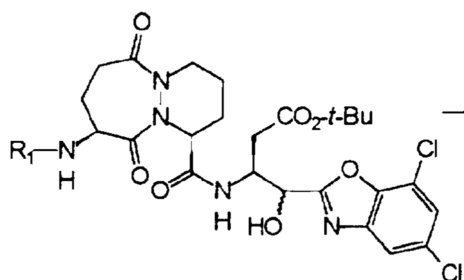
[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 4-[5-(2,6-dichlorophenyl)-oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxybutanoate (218b), was prepared from the acid **212b** and **99** in an analogous way to compound **215e** to afford a mixture of diastereomers (865mg, 80%) as a colourless solid: IR (KBr) 3298, 2974, 1723, 1659, 1544, 1518, 1430, 1394, 1370, 1328, 1273, 1256, 1156, 1134; ^1H NMR ($CDCl_3$) δ 7.45-7.28 (4H, m), 7.26-7.15 (2H, m), 5.26-5.10 (2H, m), 4.80-4.67 (1H, m), 4.59-4.42 (2H, m), 3.32-3.17 (1H, m), 2.96 (3H, 2xs), 2.93-2.79 (1H, m), 2.71-2.53

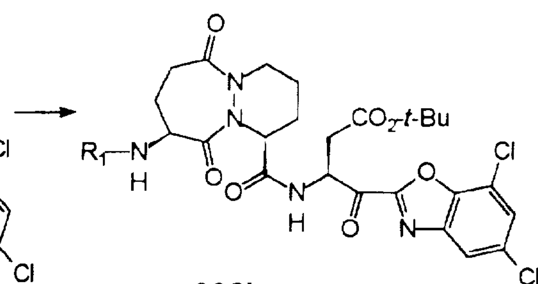
(4H, m), 2.38-2.28 (1H, m), 2.07-1.81 (4H, m); Anal. Calcd for $C_{28}H_{35}N_5Cl_2O_9S$. 0.5 H_2O: C, 48.21; H, 5.20; N, 10.03. Found: C,48.35; H, 5.26; N, 9.48. MS (ES +) 714/2/0 (M + Na, 25%), 692/90/88 (M^+ + 1, 51), 636/4/2 (38), 246 (100). Accurate mass calculated for $C_{28}H_{36}N_5Cl_2O_9S$ (MH^+): 688.1611. Found: 688.1615.

[3*S*(1*S*,9*S*)]t-Butyl 4-[5-(2,6-dichlorophenyl)-oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoate (219b), was prepared from **218b** in an analogous way to compound **216e** as an off-white powder (675mg, 81%): mp 100-200 °C; $[\alpha]_D^{24}$ -84.9 (c 1.01, CH_2Cl_2); IR (KBr) 3336, 2978, 2936, 1719, 1674, 1510, 1433, 1421, 1369, 1329, 1274, 1257, 1155, 991, 789; ^1H NMR ($CDCl_3$) δ 7.47-7.38 (4H, m), 7.24 (1H, d), 5.61-5.53 (1H, m), 5.48 (1H, d), 5.38-5.30 (1H, m), 4.67-4.45 (2H, m), 3.48-3.18 (2H, m), 3.04-2.90 (2H, m), 2.97 (3H, s), 2.69-2.54 (1H, m), 2.42-2.32 (1H, m), 2.22-2.15 (1H, m), 2.07-1.93 (3H, m), 1.71-1.65 (2H, m), 1.38 (9H, s); Anal. Calcd for $C_{28}H_{33}N_3Cl_2O_9S$: C, 48.98; H, 4.84; N, 10.20; S, 4.67. Found: C, 48.73; H, 4.95; N, 9.65; S, 4.54. MS (ES +) 692/90/88 (M^+ + 1, 100%), 636/4/2 (71). Accurate mass calculated for $C_{28}H_{34}N_5Cl_2O_9S$ (MH^+): 686.1454. Found: 686.1474.

[3*S*(1*S*,9*S*)] 4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (220b), was prepared from **219b** in an analogous way to compound **217e** as a pale cream powder (396mg, 87%): mp 100-200 °C; $[\alpha]_D^{27}$ -

129 (c 0.12, MeOH); IR (KBr) 3310, 3153, 1713, 1667, 1557, 1510, 1432, 1421, 1329, 1273, 1258, 1221, 1193, 1153, 1134, 992, 789; ^{1}H NMR (d^6 DMSO) δ 7.88 (1H, s), 7.81-7.60 (4H, m), 5.49-5.28 (1H, m), 5.24-5.14 (1H, m), 4.46-4.22 (2H, m), 3.30-3.03 (2H, m), 2.97-2.76 (3H, m), 2.96 (3H, s), 2.46-2.24 (1H, m), 2.16-2.05 (1H, m), 2.03-1.78 (3H, m), 1.68-1.46 (2H, m); MS (ES-) 632/30/28 (M - 1, 68%), 149/7/5 (100). Accurate mass calculated for $C_{24}H_{26}N_5Cl_2O_9S$ (MH^+): 630.0828. Found: 630.0852.



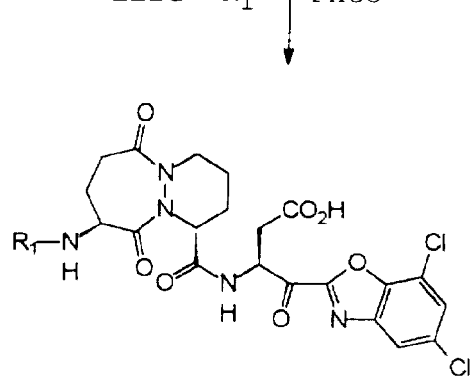


221b R_1 = $MeSO_2$

221e R_1 = PhCO

222b R_1 = $MeSO_2$

222e R_1 = PhCO



223b R_1 = $MeSO_2$

223e R_1 = PhCO

[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 4-(5,7-dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-

[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxybutanoate (221b), was prepared from the acid **212b** and (3*S*,4*RS*) t-butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (**204**) by an analogous method as that used for compound **215e** to afford a mixture of diastereomers (460mg, 70%) as a glass: IR (film) 3325, 1725, 1664, 1453, 1399, 1373, 1327, 1274, 1256, 1155; ^{1}H NMR ($CDCl_3$) δ 7.57 (1H, m), 7.36 (2H, m), 6.06 (1H, t), 5.29 (2H, m), 4.79 (1H, m), 4.47 (1H, m), 3.23 (1H, m), 2.97 and 2.94(3H combined, 2 x s), 2.9-2.4 (4H, m), 2.30 (1H, m), 1.96 (4H, m), 1.41 and 1.37 (9H combined, 2 x s). MS ES Da/e 660 $(M - 1)^-$ Cl^{35} 100%, 662 $(M - 1)^-$ Cl^{37}.

[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-hydroxybutanoate (221e), was prepared from the acid (**212e**) and (3*S*,4*RS*) t-butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (**204**) by an analogous method as that used for compound **215e** to afford a mixture of diastereomers (613mg, 87%) as a glass: IR (film) 3328, 1729, 1660, 1534, 1454, 1422, 1399, 1276, 1254, 1155; ^{1}H NMR ($CDCl_3$) δ 7.80 (2H, d), 7.60-7.35 (5H, m), 7.05 (2H, m), 5.13 (3H, m), 4.74 (1H, m), 4.51 (1H, m), 3.25 (1H, m), 3.1-2.6 (5H, m), 2.33 (1H, m), 2.1-1.5 (5H, m), 1.43 and 1.41 (9H combined, 2 x s). MS ES^+ Da/e 688 $(M + 1)^+$ Cl^{35} 55%, 690 $(M + 1)^+$ Cl^{37} 35%, 328 100%.

[3*S*(1*S*,9*S*)]t-Butyl 4-(5,7-dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-

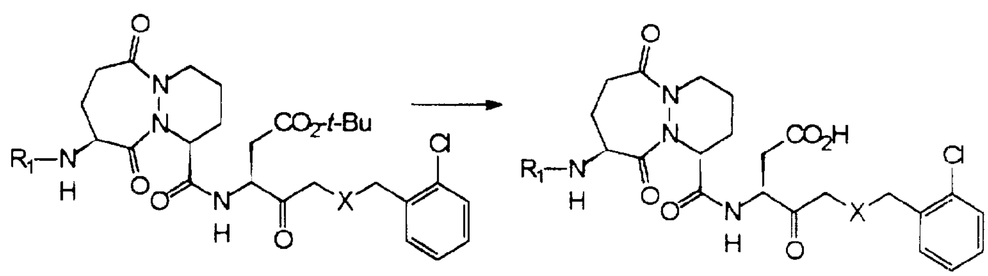
octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoate (222b), was prepared from **221b** by an analogous method as that used for compound **216e** to afford a colourless glass (371mg, 86%): $[\alpha]_D^{26}$ -81.0 (c 0.1, CH_2Cl_2); IR (KBr) 3324, 2979, 2936, 1726, 1664, 1394, 1370, 1328, 1155, 991; ^{1}H NMR ($CDCl_3$) δ 7.78 (1H, d), 7.57 (2H, m), 5.87 (1H, d), 5.69 (1H, m), 5.47 (1H, m), 4.55 (2H, m), 3.24 (2H, m), 3.0 (5H, m + s), 2.59 (1H, m), 2.39 (1H, m), 2.2 - 1.7 (4H, m), 1.65 (1H, m), 1.40 (9H, s).

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxobutanoate (222e), was prepared from **221e** by an analogous method as that used for compound **216e** to afford a colourless glass (480mg, 84%): $[\alpha]_D^{25}$ -86.4 ° (c 0.1 CH_2Cl_2); IR (KBr) 3337, 2978, 2938, 1728, 1657, 1534, 1456, 1422, 1395, 1370, 1277, 1250, 1154; ^{1}H NMR ($CDCl_3$) δ 7.80 (3H, m), 7.50 (4H, m), 7.20 (1H, d), 7.02 (1H, d), 5.60 (1H, m), 5.28 (1H, m), 5.15 (1H, m), 4.11 (1H, m), 3.34 (2H, m), 2.96 (3H, m), 2.40 (1H, m), 2.20 (1H, m), 1.92 (2H, m), 1.67 (2H, m), 1.38 (9H, s). MS ES^- Da/e 684 $(M - 1)^-$ Cl^{35} 47%, 686 $(M - 1)^-$ Cl^{37} 32%.

[3*S*(1*S*,9*S*)] 4-(5,7-Dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (223b), was prepared from **222b** by an analogous method as that used for compound **217e** to afford an off-white solid (257mg, 78%): $[\alpha]_D^{25}$ -105.7 ° (c 0.1, CH_2Cl_2); IR (KBr) 3321,

1723, 1663, 1407, 1325, 1151, 992; ^{1}H NMR (D_6-DMSO) δ 8.96 (1H, d), 8.18 (1H, d), 7.96 (1H, d), 5.50 (1H, m), 5.15 (1H, m), 4.30 (2H, m), 3.06 (2H, m), 2.87 (5H, m + s), 2.29 (1H, m), 1.99 (4H, m), 1.56 (2H, m).

[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxobutanoic acid (223e), was prepared from **222e** by an analogous method as that used for compound **217e** to afford a pale cream solid (311mg, 78%): mp 167-180 °C; $[\alpha]_D^{23}$ -88.6 ° (c 0.1 CH_2Cl_2); IR (KBr) 3331, 1724, 1658, 1534, 1458, 1421, 1279, 1256, 991; ^{1}H NMR ($CDCl_3$) δ 7.77 (4H, m), 7.4 (5H, m), 5.57 (1H, bs), 5.33 (1H, bs), 5.47 (1H, q), 4.56 (1H, bd), 3.60 (2H, m), 3.20 (3H, m), 2.76 (1H, m), 2.36 (1H, dd), 2.0 (3H, m), 1.66 (1H, m). MS ES Da/e 628 $(M - 1)^-$ Cl^{35} 7%, 630 $(M - 1)^-$ Cl^{37} 2.3%, 584 100%.



224e R_1 = PhCO, X = S   **226e** R_1 = PhCO, X = S

225e R_1 = PhCO, X = O   **227e** R_1 = PhCO, X = O

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenyl)methylthio-4-oxopentanoate (224e). 1-Hydroxybenzotriazole (0.23g,

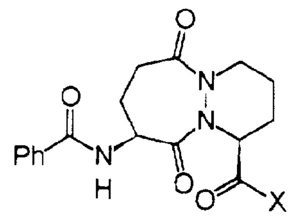
1.71mmol) and ethyl dimethylaminopropyl carbodiimide hydrochloride was added to a stirred solution of the acid **212e** (0.295g, 0.853mmol) in THF (5ml). After 5min water (0.5ml) was added followed, after a further 7min, by the addition of a solution of (3*S*) t-butyl-3-allyloxycarbonylamino-5-(2-chloro-phenyl)methylthio-4-oxopentanoate (**123**, 0.478g, 1.02mmol) and $(PPh_3)_2PdCl_2$ (20mg) in THF (2ml). Tributyltin hydride (0.65ml, 2.33mmol) was added dropwise during 20min. The mixture was kept for 4.5h then diluted with EtOAc, washed with 1M HCl, brine, sat. aq. $NaHCO_3$ and then brine again. The mixture was dried ($MgSO_4$) and concentrated. The residue was triturated several times with hexane, which was decanted and discarded, then purified by flash chromatography (10-100% EtOAc in CH_2Cl_2) to afford 0.2g (35%) of a white glassy solid: mp 70-72 °C; $[\alpha]_D^{26}$ -82.5 ° (c 0.02, CH_2Cl_2). IR (KBr) 3404, 1726, 1660, 1534, 1524, 1422, 1277, 1254, 1154; ^1H NMR ($CDCl_3$) δ 7.83-7.78 (2H, m), 7.7, 7.75-7.32, 7.26-7.20 (7H, 3m), 7.12 (1H, d, *J* = 8.2), 7.01 (1H, d, *J* = 7.3), 5.23-5.08 (2H, m), 5.03-4.94 (1H, m), 4.62 (1H, dt, *J* = 14.5), 3.78 (2H, m), 3.38-3.29 (1H, m), 3.26 (2H, s), 3.06-2.82 (4H, m), 2.71 (1H, dd, *J* = 17.2, 4.5), 2.39 (1H, dd, *J* = 13.2, 6.5), 2.15-1.83, 1.73-1.63 (5H, m), 1.45 (9H, s). Anal. Calcd for $C_{33}H_{39}ClN_4O_7S$: C, 59.05; H, 5.86; N, 8.35. Found: C, 59.00; H, 5.80; N, 7.92.

[*3RS*, (1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenylmethyloxy)-4-oxopentanoate (225e), was prepared from acid **212e** and (3*S*) t-butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethyloxy)-4-oxopentanoate (**201**) using a

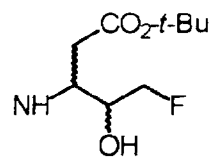
method similar to that used for compound **224e**, to afford 40mg (23%) of a glassy solid: ^{1}H NMR ($CDCl_3$) δ 7.83-7.73 (2H, m), 7.67-7.10 (9H, m), 5.23-5.09 (2H, m), 4.59 (1H, m), 4.45-4.22 (2H, m), 3.7-3.19, 3.08-2.72, 2.71-2.47, 2.05-1.85, 1.72-1.61, 1.45-1.26 (20H, 6m).

[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenyl)methylthio-4-oxopentanoic acid (226e), was prepared from **224e** by an analogous method as that used for compound **217e** which afforded 0.22g (81%) of an off-white solid: mp 95-100 °C; $[\alpha]_D^{23}$ -95.6 ° (c 0.2, CH_2Cl_2). IR (KBr) 3393, 1720, 1658, 1529, 1422, 1279; ^{1}H NMR (D_6-DMSO) δ 8.80 (1H, d, *J* = 7.5), 7.89 (2H, m), 7.7 (1H, d, *J* = 7.7), 7.56-7.28 (7H, m), 5.10 (1H, m), 4.87-4.73 (2H, m), 4.39 (1H, m), 3.77 (2H, m), 3.44, 3.35 (2H, +H_2O, 2m), 2.97-2.56, 2.2, 1.92, 1.61 (11H, 4m). Anal. Calcd for $C_{29}H_{31}ClN_4O_7S$ 0.5H_2O: C, 55.02; H, 5.10; N, 8.85. Found: C, 55.00; H, 5.09; N, 8.71.

[3*RS*, (1*S*,9*S*)] 3-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenylmethyloxy)-4-oxopentanoic acid (227e), was prepared from **225e** by an analogous method as that used for compound **217e**. The product was further purified by flash chromatography (0-5% MeOH/CH_2Cl_2) to afford 19mg (81%) of a glassy solid: ^{1}H NMR ($CDCl_3$) δ 7.79 (2H, m), 7.66-7.18 (9H, m), 5.30-5.10 (2H, m), 4.85 (1H, m), 4.65 (2H, m), 4.53 (1H, m), 4.28 (2H, m), 3.28, 3.01, 2.72, 2.33, 1.94, 1.60 (11H, 6m). MS (ES^-, m/z) 597 (M^+ - 1, 100%).



228e X =



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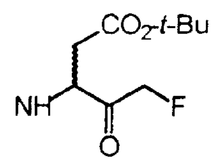
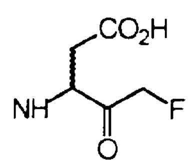


230e X =



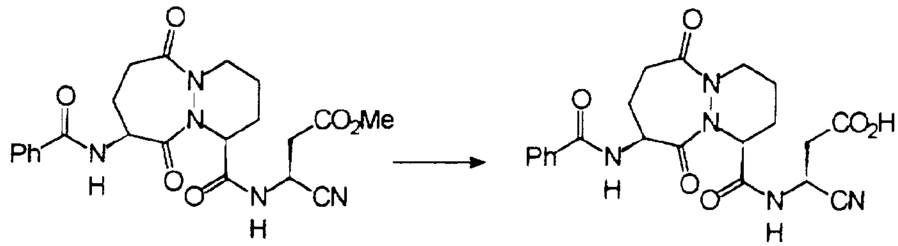
[*3RS*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-(228e). 1-Hydroxybenzotriazole (0.23g, 1.68mmol) followed by ethyldimethylaminopropyl carbodiimide hydrochloride (0.21g, 1.09mmol) were added to a stirred solution of the acid **212e** (0.29g, 0.84mmol) in CH_2Cl_2 (3ml) at rt. The mixture was kept for 10min then a solution of (3*RS*,4*RS*) t-butyl 3-amino-5-fluoro-4-hydroxypentanoate (Revesz, L. et al. <u>Tetrahedron Lett.</u>, 52, pp. 9693-9696 (1994); 0.29g, 1.40mmol) in CH_2Cl_2 (3ml) was added followed by 4-dimethylaminopyridine

(10mg). The solution was stirred for 17h, diluted with EtOAc, washed with 1M HCl, brine, sat. aq. $NaHCO_3$ and brine again, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (50-100% EtOAc/CH_2Cl_2 and 5% MeOH/EtOAc) to afford 0.25g (56%) of a white glassy solid: IR (KBr) 3343, 1726, 1658, 1536, 1426, 1279, 1257, 1157; ^1H NMR ($CDCl_3$) δ 7.84-7.79 (2H, m), 7.57-7.40 (3H, m), 7.05-6.92, 6.73 (2H, 2m), 5.17-5.04 (2H, m), 4.56, 4.35-4.21, 4.04 (5H, 3m), 3.36, 3.09-2.34, 2.00 (11H, 3m), 1.46 (9H, s). Anal. Calcd for $C_{26}H_{35}FN_4O_7$ $0.5H_2O$: C, 57.45; H, 6.65; N, 10.31. Found: C, 57.64; H, 6.56; N, 10.15.

[*3RS*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-oxypentanoate (229e) was prepared from **228c** by an analogous method to that used for compound **216e**. After purification by flash chromatography (30-50% EtOAc/CH_2Cl_2) the product was obtained as a white glassy solid (0.194g, 89%): IR (KBr) 3376, 1728, 1659, 1529, 1424, 1279, 1256, 1156.

[*3RS*, (1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-oxopentanoic acid (230e), was prepared from **229e** by an analogous method to that used for compound **217e** to afford **230e** as a white glassy solid (100%): mp 105-125 °C; $[\alpha]_D^{23}$ -91.4 ° (c 0.72, CH_3OH). IR (KBr) 3336, 1789, 1737, 1659, 1535, 1426, 1279, 1258, 1186; ^1H NMR (CD_3OD) δ 7.71-7.68 (2H, m), 7.37-7.23 (3H, m), 5.02, 4.88-4.63,

4.37-4.0 (6H, 3m), 3.30, 2.97, 2.68-2.60, 2.37-1.54 (11H, 4m). MS(ES^-, m/z) 475 (M^+ - 1, 100%).

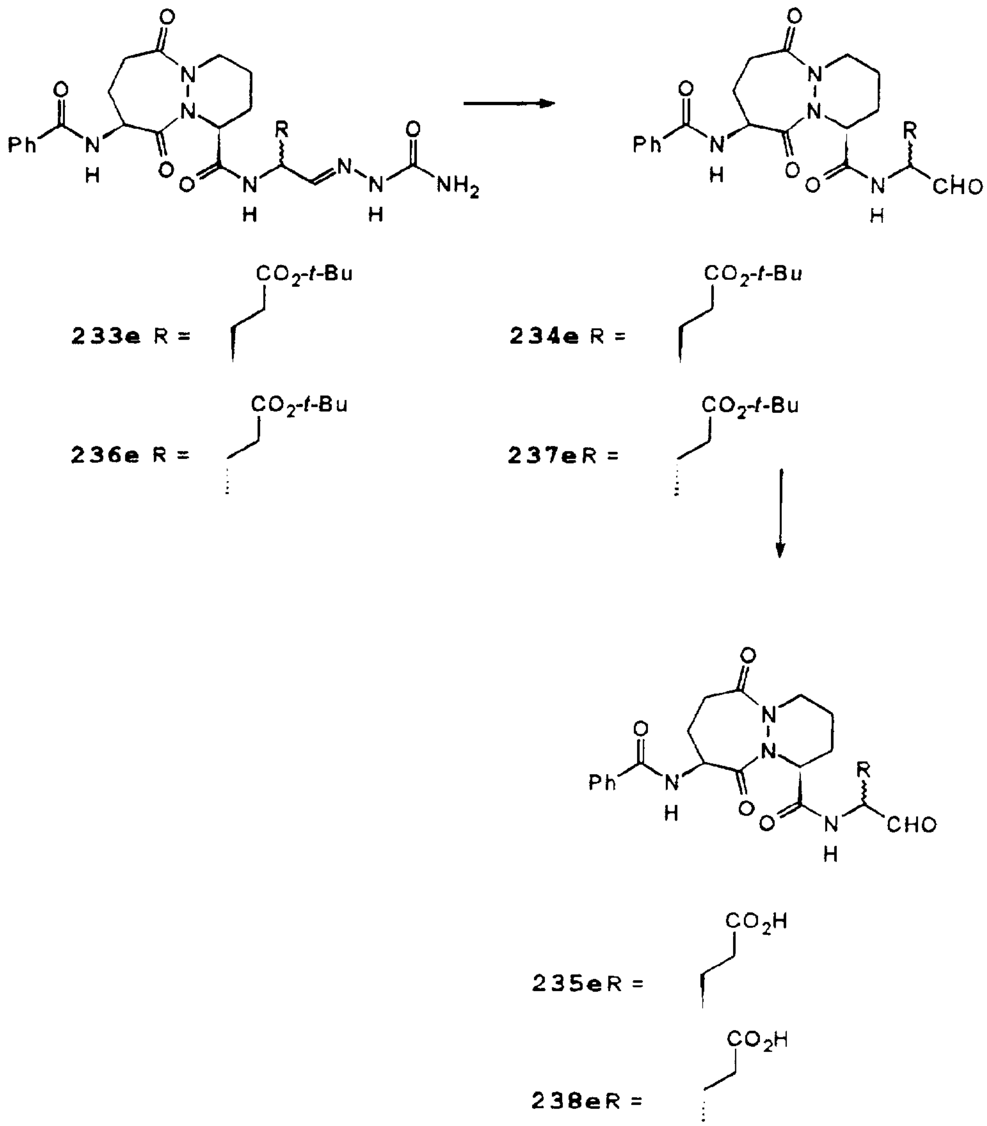


(231e) (232e)

[3*S*(1*S*,9*S*)]-Methyl 9-(benzoylamino)-3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-3-cyanopropanoate (231e). N-Fluorenylmethyloxy-carbonyl-3-amino-3-cyanopropionic acid methyl ester (EP0547699A1, 385mg, 1.1mmol) was treated with 17ml of diethylamine. After 1.5h stirring at room temperature the solution was concentrated. The residue was chromatographed on silica gel (3% methanol in CH_2Cl_2) and gave the free amine as a pale yellow oil. To a solution of this oil and hydroxybenzotriazole (297mg, 2.19mmol) in DMF (5ml), was added at 0 °C ethyldimethylaminopropyl carbodiimide (232mg, 1.21mmol, 1.1 equiv) followed by (1*S*,9*S*) 9-(benzoylamino)-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (**212e**). After stirring at 0 °C for 5 min and then at room temperature overnight, the mixture was diluted with CH_2Cl_2 (50ml) and the resulting solution washed successively with 1M HCl (2 x 30ml), H_2O (30ml), 10% $NaHCO_3$ (2 x 30ml) and sat. aq. NaCl, dried ($MgSO_4$) and concentrated. Purification by flash

chromatography on silica gel (3% methanol in CH_2Cl_2) afforded the compound **231e** (404mg, 83%) as a solid: $[\alpha]_D^{20}$ -121 ° (c 0.14, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.40-7.83 (5H, m), 7.38 (1H, d), 6.96 (1H, d), 5.27-5.07 (2H, m), 4.66-4.50 (1H, m), 3.79 (3H, s), 3.23-2.73 (6H, m), 2.47-2.33 (1H, m), 2.15-1.82 (4H, m); Anal. Calcd for $C_{22}H_{25}N_5O_6$: C, 58.0; H, 5.53; N, 15.38. Found: C, 57.6; H, 5.6; N, 15.0.

[3*S*(1*S*,9*S*)] 9-(Benzoylamino)-3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-3-cyanopropanoic acid (232e). A solution of methyl ester **231e** (400mg, 0.88mmol) in methanol (30ml) and water (30ml) was cooled at 0 °C and treated with diisopropylethylamine. The solution was stirred at 0 °C for 10min and then at room temperature overnight. The heterogeneous mixture was concentrated and the solid obtained was chromatographed on silica gel (5% methanol/1% formic acid in CH_2Cl_2) affording the free acid **232e** (170mg, 44%) as a white solid: mp 155 °C (dec); $[\alpha]_D^{20}$ -117 ° (c 0.1, MeOH); IR (KBr) 3343, 3061, 2955, 1733, 1656, 1577, 1533, 1490, 1421, 1342, 1279, 1256, 1222, 1185, 708; ^1H NMR (D^4-MeOH) δ 7.88-7.28 (5H, m), 5.20-5.03 (1H, m), 4.98-4.84 (2H, m), 4.75-4.53 (1H, m), 4.51-4.34 (1H, m), 3.45-3.22 (1H, m), 3.14-2.94 (1H, m), 3.14-2.94 (1H, m), 2.88-2.61 (2H, m), 2.53-1.50 (8H, m); Anal. Calcd for $C_{21}H_{23}N_5O_6 \cdot 1.5H_2O$: C,53.84; H, 5.59; N, 14.95; O, 25.61. Found: C, 54.3; H, 5.4; N, 14.3.



[4*S*, (1*S*,9*S*)] t-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate semicarbazone (233e). A solution of (1*S*,9*S*) 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(benzoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (**212e**) (345mg, 1.0mmol), (4S) t-butyl N-

(allyloxycarbonyl)-4-amino-5-oxopentanoate semicarbazone (**208a**) (361mg, 1.1mmol, 1.1 equiv) and $(Ph_3P)_2PdCl_2$ (20mg) in CH_2Cl_2 (5ml), was treated dropwise with n-Bu_3SnH (0.621ml, 2.3mmol, 2.1 equiv). The resulting orange brown solution was stirred at 25 °C for 10min and then 1-hydroxybenzotriazole (297mg, 2.2mmol, 2 equiv) was added. The mixture was cooled to 0 °C and ethyldimethylaminopropyl carbodiimide (253mg, 1.3mmol, 1.2 equiv) added. After stirring at 0 °C for 10min and then at room temperature overnight, the mixture was diluted with EtOAc (50ml) and the resulting solution washed successively with 1M HCl (3 x 25ml), 10% $NaHCO_3$ (3 x 25ml) and sat. aq. NaCl, dried ($MgSO_4$) and concentrated. Flash chromatography on silica gel (2-10% methanol in CH_2Cl_2) afforded compound **233e** (280mg, 49%) as a tan solid: $[\alpha]_D^{20}$ -95 (c 0.09, MeOH); IR (KBr) 3477, 3333, 2968, 2932, 1633, 1580, 1535, 1423, 1378, 1335, 1259, 1156, 1085, 709; ^{1}H NMR ($CDCl_3$) δ 9.32 (1H, s), 7.83-7.39 (6H, m), 7.11-7.09 (1H, m), 6.30-5.30 (2H, brs), 5.17-5.05 (2H, m), 4.62-4.38 (2H, m), 3.30-3.15 (1H, m), 3.13-2.65 (2H, m), 2.46-2.19 (3H, m), 2.15-1.54 (8H, m), 1.42 (9H, s).

[4*R*, (1*S*,9*S*)] t-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate semicarbazone (236e), was prepared by an analogous method to that used for **233e** using (4*R*) t-butyl N-allyloxycarbonyl-4-amino-5-oxo-pentanoate semicarbazone (**208b**, 435mg, 1.33mmol). The product was obtained as a foam (542mg, 71%): $[\alpha]_D^{20}$ -99 ° (c 0.19, $CHCl_3$); IR (KBr) 3473, 3331, 3065, 2932, 2872, 1660, 1580, 1533, 1488, 1423, 1370, 1337, 1278, 1254, 1223, 1155, 1080,

1024, 983, 925, 877, 846, 801, 770, 705; ^{1}H NMR ($CDCl_3$) δ 9.42 (1H, s), 7.81 (2H, d), 7.51-7.40 (4H, m), 7.06 (1H, d), 6.50-5.50 (2H, broad s), 5.25-5.00 (2H, m), 4.60-4.45 (2H, m), 3.15-2.85 (2H, m), 2.75-2.35 (1H, m), 2.30-1.23 (11H, m), 1.42 (9H, s).

[4*S*, (1*S*,9*S*)] t-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate (234e). A solution of semicarbazone **233e** (390mg, 0.68mmol) in methanol (10ml) was cooled at 0 °C and then treated with a 38% aq. solution of formaldehyde (2ml) and 1M HCl (2ml). The reaction mixture was then stirred overnight at room temperature. The solution was concentrated to remove the methanol. The aq. solution was extracted with EtOAc (30ml). The organic solution was successively washed with 10% $NaHCO_3$ (30ml) and sat. aq. NaCl (30ml), dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (2-5% methanol in CH_2Cl_2) afforded **234e** (179mg, 51%) as a white foam: $[\alpha]_D^{20}$ -101 ° (c 0.064, MeOH); IR (KBr) 3346, 2976, 2934, 1730, 1657, 1535, 1456, 1425, 1278, 1255, 1156, 708; ^{1}H NMR ($CDCl_3$) δ 9.56 (1H, s), 7.88-7.38 (5H, m), 7.01 and 6.92 (2H, 2d), 5.27-5.08 (2H, m), 4.69-4.46 (1H, m), 3.50-3.27 (2H, m), 3.15-2.73 (2H, m), 2.46-1.83 (10H, m), 1.45 (9H, s).

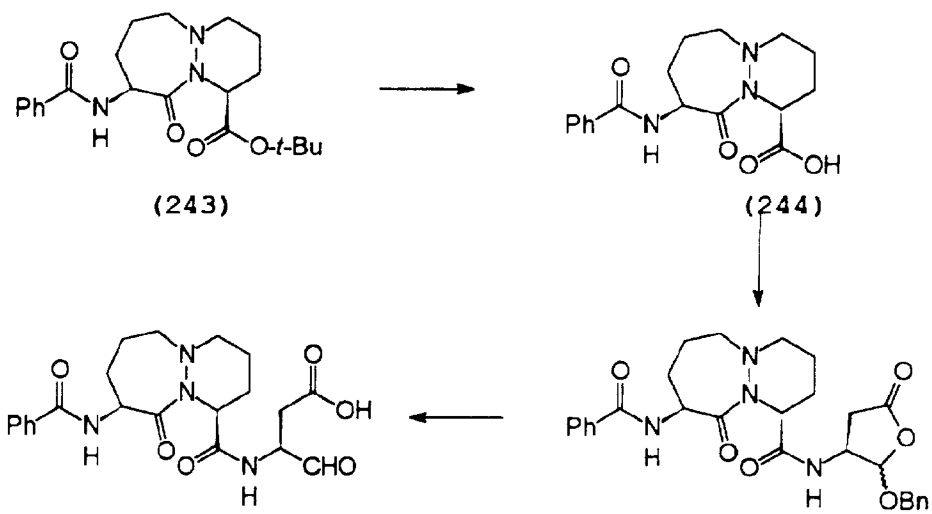
[4*R*, (1*S*,9*S*)] t-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate (237e), was prepared from **236e** by an analogous method to **234e** to afford a white foam (390mg, 85%): $[\alpha]_D^{20}$

-113 ° (c 0.242, $CHCl_3$); IR (KBr) 3352, 3065, 2974, 1729, 1657, 1536, 1489, 1454, 1423, 1369, 1338, 1278, 1255, 1223, 1156, 1078, 1026, 981, 846, 709.

[4*S*, (1*S*,9*S*)] 4-[9-(Benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoic acid (235e). A solution of t-butyl ester **234e** (179mg, 0.35mmol) in dry CH_2Cl_2 (3ml) was cooled to 0 °C and treated with trifluoroacetic acid (2ml). The resulting solution was stirred at 0 °C for 30min and then at room temperature for 2h. The solution was concentrated, the residue taken up in dry CH_2Cl_2 (5ml) and the mixture again concentrated. This process was repeated once again with more CH_2Cl_2 (5ml). The residue obtained was crystallized in diethyl ether. The precipitate was collected and purified on silica gel column (5% methanol in CH_2Cl_2) which afforded compound **235e** as a white solid (111mg, 70%): mp 142 °C (dec); $[\alpha]_D^{20}$ -85.5 (c 0.062, MeOH); IR (KBr) 3409, 3075, 2952, 1651, 1541, 1424, 1280, 1198, 1136, 717; ^1H NMR (D_6-DMSO) δ 9.40 (1H, s), 8.62 (2H, m), 7.96-7.38 (5H, m), 5.19-5.02 (1H, m), 4.98-4.79 (1H, m), 4.48-4.19 (1H, m), 3.51-3.11 (2H, m), 3.04-2.90 (2H, m), 2.38-1.46 (10H, m).

[4*R*, (1*S*,9*S*)] 4-[9-(Benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoic acid (238e), was prepared from **237e** by an analogous route to **235e** which afforded a beige foam (190mg, 60%): $[\alpha]_D^{20}$ -78 (c 0.145, MeOH); IR (KBr) 3400, 3070, 2955, 2925, 2855, 1653, 1576, 1541, 1490, 1445, 1427, 1342, 1280, 1258, 1205, 1189, 1137, 1075, 1023, 983, 930,

878, 843, 801, 777, 722; ^{1}H NMR (D_6-DMSO) δ 9.40 (1H, s), 8.72-8.60 (2H, m), 7.89 (2H, d), 7.56-7.44 (3H, m), 5.17 (1H, m), 4.90-4.83 (1H, m), 4.46-4.36 (1H, m), 4.20-4.15 (1H, m), 3.40-3.30 (1H, m), 2.98-2.90 (2H, m), 2.50-1.60 (10H, m).



(243) (244) (246) (245)

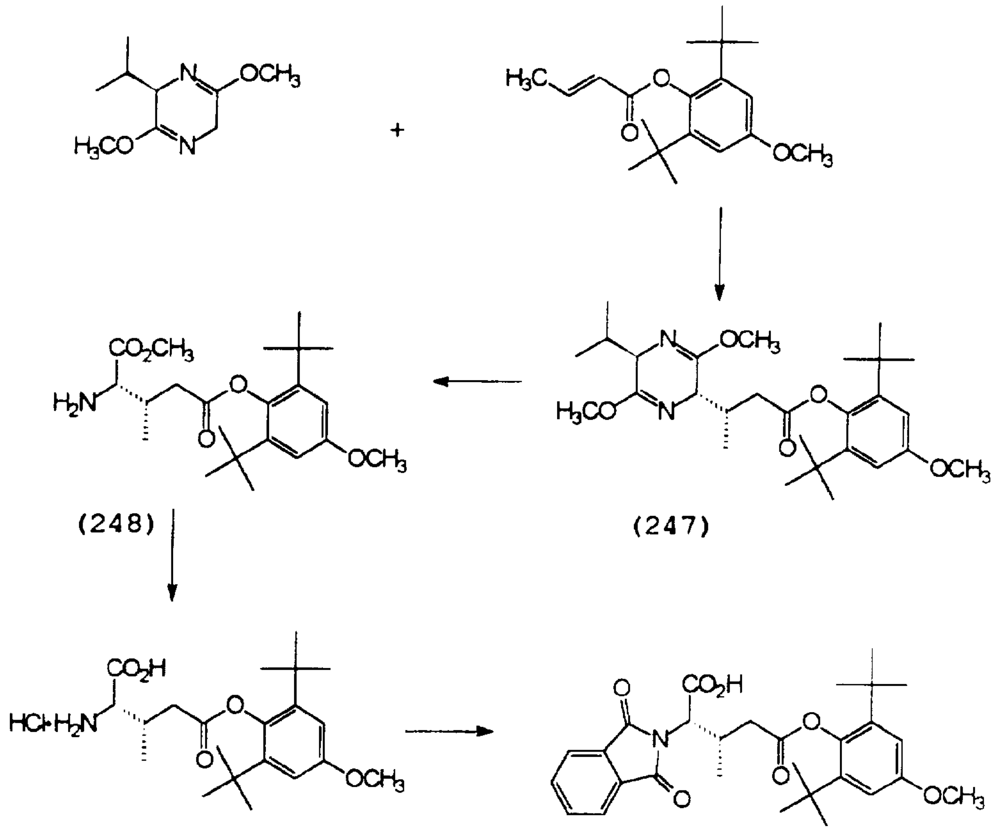
(1*S*,9*S*) t-Butyl 9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (243), was prepared from (1*S*,9*S*) t-butyl 9-amino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (Attwood, et al. J. Chem. Soc., Perkin 1, pp. 1011-19 (1986)), by the method described for **211e**, to afford 2.03g (86%) of a colourless foam: $[\alpha]_D^{25}$ -15.9 ° (c 0.5, CH_2Cl_2); IR (KBr) 3400, 2976, 2937, 1740, 1644, 1537, 1448, 1425, 1367, 1154; ^{1}H NMR ($CDCl_3$) δ 7.88-7.82 (2H, m), 7.60-7.38 (4H, m), 5.48 (1H, m), 4.98 (1H, m), 3.45 (1H, m), 3.22-2.96 (2H, m), 2.64 (1H, m), 2.43-2.27 (2H, m), 1.95 (2H, m), 1.82-1.36 (4H, m), 1.50 (9H, s); Anal. Calcd for $C_{21}H_{29}N_3O_4 \cdot 0.25H_2O$: C,

64.35; H, 7.59; N, 10.72. Found: C, 64.57; H, 7.43; N, 10.62. MS (ES +, m/z) 388 (100%, M^+ + 1).

(1*S*,9*S*) 9-Benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (244), was prepared from (1*S*,9*S*) t-butyl 9-benzoylamino-octahydro-10-oxo-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (**243**), by the method described for **212e**, to afford 1.52g (89%) of a white powder: mp. 166-169 °C (dec); $[\alpha]_D^{25}$ -56.4 ° (c 0.5, CH_3OH); IR (KBr) 3361, 2963, 2851, 1737, 1663, 1620, 1534, 1195, 1179; ^1H NMR (D_6-DMSO) δ 12.93 (1H, brs), 8.44 (1H, d, *J* = 8.4), 7.93 (2H, m), 7.54 (3H, m), 5.46 (1H, m), 4.87 (1H, m), 3.12 (2H, m), 2.64 (1H, m), 2.64 (1H, m), 2.27 (1H, m), 1.98-1.68 (7H, m), 1.40 (1H, m); Anal. Calcd for $C_{17}H_{21}N_3O_4$. $0.25H_2O$: C, 60.79; H, 6.45; N, 12.51. Found: C, 61.07; H, 6.35; N, 12.55. MS (ES+, m/z) 332 (58%, M^+ + 1), 211 (100).

[3*S*,2*RS*(1*S*,9*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (245), was prepared from (1*S*,9*S*) 9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylic acid (**244**), by the method described for **213e**, to afford 601mg (76%) of a colourless foam: IR (KBr) 3401, 2945, 1794, 1685, 1638, 1521, 1451, 1120; ^1H NMR ($CDCl_3$) δ 7.87-7.77 (2H, m), 7.57-7.14 (10H, m), 5.59-5.47 (2H, m), 4.97-4.32 (4H, m), 3.27-1.35 (14H, m); Anal. Calcd for $C_{28}H_{32}N_4O_6$. $0.5H_2O$: C, 63.50; H, 6.28; N, 10.58. Found: C, 63.48; H, 6.14; N, 10.52. MS (ES +, m/z) 521 (100%, M^+ + 1).

[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide-4-oxobutanoic acid (246), was prepared from [3*S*, 2*RS* (**1*S*,9*S***)]N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**245**), by the method described for **214e**, to afford 396mg (84%) of a white powder: mp. 110-115 °C; $[\alpha]_D^{26}$ -126.3 ° (c 0.2, CH_3OH); IR (KBr) 3345, 2943, 1787, 1730, 1635, 1578, 1528, 1488, 1450, 1429; ^1H NMR (CD_3OD) δ 7.88 (2H, m), 7.48 (3H, m), 5.55 (1H, m), 4.91 (1H, m), 4.56 (1H, m), 4.29 (1H, m), 3,41-3.05 (3H, m), 2.76-2.41 (3H, m), 2.28-2.01 (3H, m), 1.86-1.65 (4H, m), 1.36 (1H, m); Anal. Calcd for $C_{21}H_{26}N_4O_6$. $1.25H_2O$: C, 55.68; H, 6.34; N, 12.37. Found: C, 55.68; H, 6.14; N, 12.16. MS (ES -, m/z) 429 (100%, M^+ - 1).



(248) (247)

(249) (250)

[(3*S*(2*R*, 5*S*)]-2,6-Di-tert-butyl-4-methoxyphenyl-3-[5-(2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazinyl)]butanoate (247). n-Butyllithium (1.6M in hexane) (22.3ml, 35.7mmol) was added dropwise over 20min to a solution of (2*R*)-(-)-2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazine (5.8ml, 6.0g, 32.4mmol) in THF (250ml) cooled to -75 °C at a rate such that the temperature was maintained below -72 °C. The reaction mixture was stirred for 1h at -75 °C and a solution of 2,6-di-t-butyl-4-methoxyphenyl-2-butenoate (Suzuck et al. Liebigs Ann. Chem. pp. 51-61 (1992))

(9.9g, 32.5mmol) in THF (60ml) was added over 30 minutes maintaining the temperature below -72 °C during the addition. The reaction mixture was kept at -75 °C for 1.5h and a solution of glacial acetic acid (6ml) in THF (25ml) was added at -75 °C and the solution warmed to room temperature. The solution was poured onto 10% NH_4Cl (300ml) and extracted with diethyl ether (3 x 250ml). The combined organic phases were washed with brine (2 x 200ml), dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residual oil was purified by flash chromatography on silica gel (20% heptane in CH_2Cl_2) which afforded the title compound as a light yellow oil (13.5g, 85%): $[\alpha]_D^{20}$ -64 ° (c 0.22, MeOH); IR (KBr) 2962, 2873, 2840, 1757, 1697, 1593, 1460, 1433, 1366, 1306, 1269, 1236, 1187, 1157, 1126, 1063, 1038, 1011, 970, 924, 892, 867, 846, 831, 797, 773, 754; ^1H NMR ($CDCl_3$) δ 6.85 (2H, s), 4.21 (1H, t, *J* = 3.5), 3.98 (1H, t, *J* = 3.5), 3.79 (3H, s), 3.71 (3H, s), 3.69 (3H, s), 3.15 (1H, dd, *J* 17.8, 7.9), 2.86-2.81 (1H, m), 2.58 (1H, dd, *J* = 17.8, 5.9), 2.28-2.19 (1H, m), 1.33 (18H, s), 1.02 (3H, d, *J* = 6.8), 0.70 (6H, dd, *J* = 13, 6.8).

(2*S*,3*S*)-5-[2,6-Di-t-butyl-4-methoxyphenyl]1-methyl-3-methylglutamate (248). A solution of [3*S*(2*R*, 5*S*)]-2,6-di-t-butyl-4-methoxyphenyl-3-[5-(2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazinyl)]butanoate (**247**) (22.4g, 45.8mmol) in acetonitrile (300ml) and 0.25N HCl (366ml, 2 equiv) was stirred at room temperature under nitrogen atmosphere for 4 days. The acetonitrile was evaporated under reduced pressure and diethylether (250ml) was added to the aq. phase. The pH of the aq. phase was adjusted to pH8-9 with concentrated ammonia

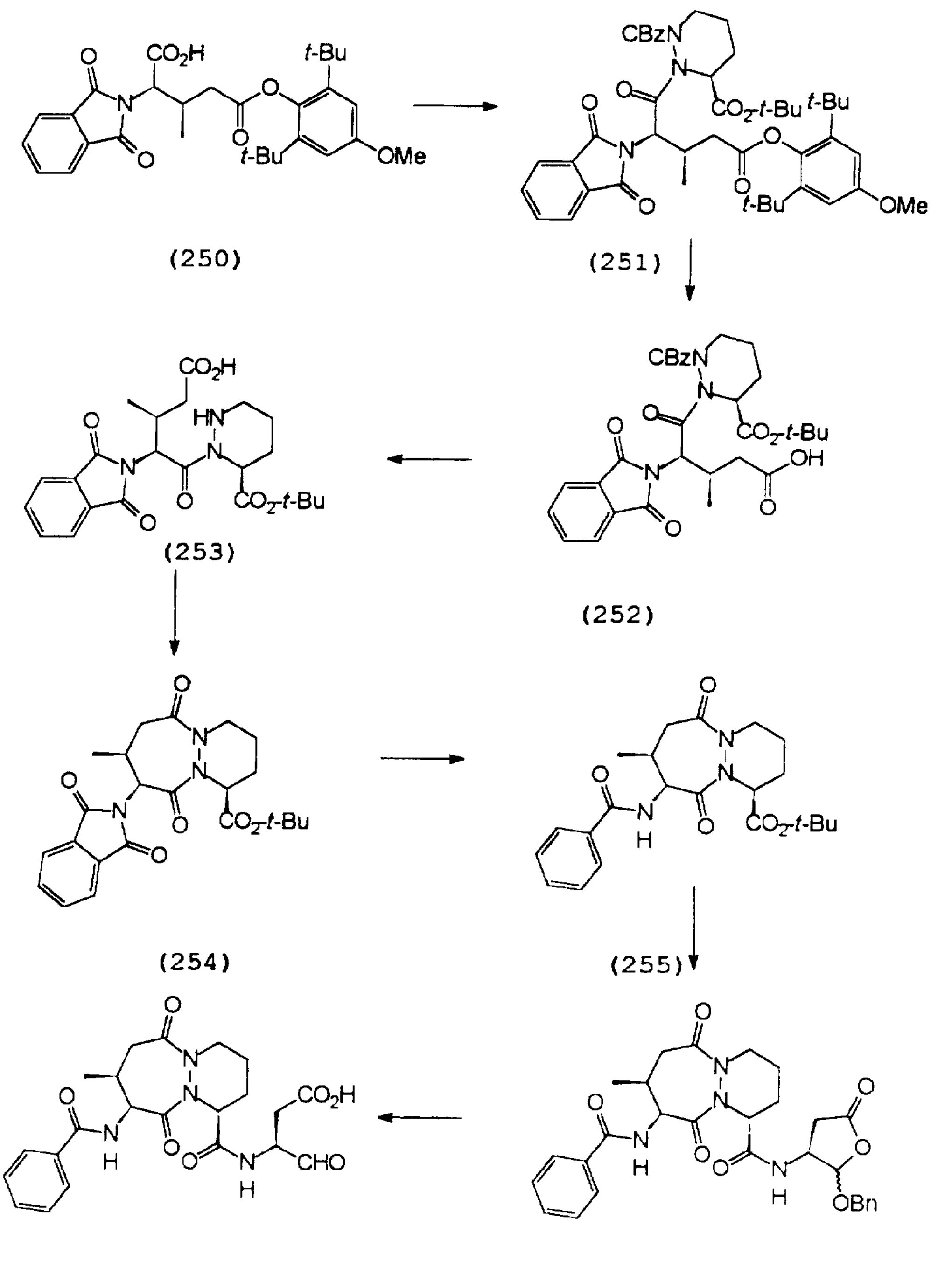
solution (32%) and the phases separated. The aq. phase was extracted with diethylether (2 x 250ml). The combined organic phases were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residual oil was purified by flash chromatography on silica gel (2% methanol in CH_2Cl_2) which afforded the required product as a light yellow oil (8.2g, 45%): $[\alpha]_D^{20}$ +20 ° (c 0.26, MeOH); IR(KBr) 3394, 3332, 3000, 2962, 2915, 2877, 2838, 1738, 1697, 1593, 1453, 1430, 1419, 1398, 1367, 1304, 1273, 1251, 1221, 1203, 1183, 1126, 1063, 1025, 996, 932, 891, 866, 847, 800, 772, 745; ^{1}H NMR ($CDCl_3$) δ 6.85 (2H, s), 3.79 (3H, s), 3.74 (3H, s), 3.72-3.69 (1H, m), 3.05-2.85 (1H, m), 2.67-2.50 (2H, m), 1.32 (18H, s), 0.93 (3H, d, J = 7); Anal. Calcd for $C_{22}H_{35}NO_5$: C, 67.15; H, 8.96; N, 3.56. Found: C, 67.20; H, 9.20; N, 3.70.

(2*S*,3*S*)-5-[2,6-Di-t-butyl-4-methoxyphenyl]3-methylglutamate (249). A solution of (2*S*,3*S*)-5-[2,6-di-t-butyl-4-methoxyphenyl]3-methylglutamate (**248**) (8.0g, 20.3mmol) in 5N HCl (200ml) was heated at reflux for 2h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in cyclohexane (x4) and evaporated to dryness (x4) which afforded a white solid (7.9g, 93%): mp 230 °C; $[\alpha]_D^{20}$ +22 ° (c 0.27, MeOH); IR (KBr) 3423, 2964, 1755, 1593, 1514, 1456, 1421, 1371, 1303, 1259, 1201, 1179, 1138, 1106, 1060, 966, 926, 861, 790, 710; ^{1}H NMR (MeOD) δ 6.76 (2H, s), 4.02 (1H, d, J = 3.7), 3.67 (3H, s), 3.05-2.85 (1H, m), 2.80-2.55 (2H, m), 1.22 (18H, s), 1.09 (3H, d, J = 6.3); ^{13}C NMR (MeOD) δ 174.5, 171.4, 158.6, 145.2, 143.1, 113.2, 58.3, 56.3, 39.8, 36.9,

32.5, 16.6; Anal. Calcd for $C_{21}H_{34}ClNO_5$: C, 60.64; H, 8.24; N, 3.37. Found: C, 60.80; H, 8.40; N, 3.40.

(2*S*,3*S*)-5-[2,6-Di-t-butyl-4-methoxyphenyl]3-methyl-2-phthalimido-1,5-pentanedioate (250),

Diisopropylethylamine (4.1ml, 3.04g, 23.5mmol, 1.25 equiv) and phthalic anhydride (3.5g, 23.6mmol, 1.25 equiv) were added to a solution of (2*S*,3*S*)-5-[2,6-di-t-butyl-4-methoxyphenyl]3-methylglutamate (**249**) (7.8g, 18.6mmol) in toluene (300ml). and the resulting mixture was heated at reflux for 3 hours. After cooling to room temperature, the reaction mixture was evaporated to dryness and the resulting oil purified by flash chromatography on silica gel (2% methanol in CH_2Cl_2) which afforded the required product as a white foam (8.35g, 87%): $[\alpha]_D^{20}$ -20 ° (c 1.04, MeOH); IR (KBr) 3480, 2968, 2880, 1753, 1721, 1594, 1462, 1422, 1388, 1303, 1263, 1216, 1183, 1148, 1062, 1003, 933, 899, 755, 723; ^{1}H NMR ($CDCl_3$) δ 7.92-7.87 (2H, m), 7.78-7.73 (2H, m), 6.84 (2H, s), 4.95 (1H, d), 3.78 (3H, s), 3.30-3.05 (2H, m), 2.85-2.65 (1H, m), 1.30 (18H, s), 1.13 (3H, d).



(250) (251) (252) (253) (254) (255) (256) (257)

1-(2,6-di-t-Butyl-4-methoxy)-phenyl-5-(1-benzyloxycarbonyl-3-t-butoxycarbonyl-hexahydro-pyridazin-2-yl)-3-methyl-4-phthalimidopentan-1,5-dioate (251). A solution of the amino acid (**250**) (1.2g, 2.35mmol) in dry diethylether (10ml) was treated with phosphorus pentachloride (0.52g, 2.5mmol) at room temperature for 2h. The mixture was concentrated and treated several times with toluene and again evaporated to dryness. The resulting acid chloride was dissolved in dry THF (5ml) and CH_2Cl_2 (5ml) and cooled to 0 °C. t-Butyl-1-(benzyloxycarbonyl)-hexahydro-3-pyridazine-carboxylate (0.753g, 2.35mmol, 1 equiv) and N-ethylmorpholine (3ml) were added to the solution. The reaction mixture was stirred for 30min at 0 °C and then overnight at room temperature. The mixture was evaporated and the resulting residue taken up with CH_2Cl_2 (30ml). The solution was washed with 1M HCl, water, 10% $NaHCO_3$, dried ($MgSO_4$) and evaporated. The resulting white foam was purified on silica gel (0-2% methanol in CH_2Cl_2) which afforded the required compound **251** as a pale yellow glassy solid (740mg, 39%): $[\alpha]_D^{20}$ -22 (c 0.42, MeOH); IR (KBr) 3441, 2966, 1725, 1693, 1386, 1255, 1221, 1186, 1154, 1123, 1063, 724; ^{1}H NMR ($CDCl_3$) δ 7.94-7.89 (4H, m), 7.56-7.28 (5H, m), 6.84 (2H, 2s), 5.29-5.20 (2H, AB), 4.91-4.81 (1H, m), 4.05-3.88 (1H, m), 3.78 (3H, s), 3.75-3.80 (1H, m), 3.28-2.95 (2H, m), 2.23-1.51 (6H, m), 1.45 (9H, s), 1.31 (9H, s), 1.28 (9H, s), 1.27 (3H, d).

(1*S*, 8*S*, 9*S*) t-Butyl 6,10-dioxo-8-methyl-1,2,3,4,7,8,9,10-octahydro-9-phthalimido-6H-pyridazino[1,2-a][1,2]diazepin-1-carboxylate (254). A solution of the protected acid (**251**) (715mg, 0.893mmol)

in acetonitrile was treated with Cerium (IV) ammonium nitrate (1.8g, 3.3mmol, 3.7 equiv) in water (3ml) for 4h at room temperature. Mannitol (600mg, 3.3mmol, 3.7 equiv) was added and the mixture was stirred for 1h. Diethylether (50ml) and water (30ml) were added to the mixture. After decantation, the aq. phase was extracted with diethylether (4 x 50ml). The combined organic phase was washed with water, dried ($MgSO_4$) and concentrated. Chromatography on silica gel (10% methanol in CH_2Cl_2) afforded 5-(1-benzyloxycarbonyl-3-t-butoxycarbonyl-hexahydropyridazin-2-yl)carbonyl-3-methyl-4-phthalimidopentanoic acid (**252**) (360mg, 64%): $[\alpha]_D^{20}$ -49.2 c 0.118, MeOH). This product was used without further purification (360mg, 0.609mmol), and was hydrogenated in methanol (30ml) using 10% Pd/carbon (36mg) for 3h. The reaction mixture was filtered and the resulting solution concentrated to afford the amine (**253**) as a foam (270mg, 96%) $[\alpha]_D^{20}$ -56.1 (c 0.18 MeOH). The amine (**253**) was dissolved in dry THF (10ml) and phosphorous pentachloride (305mg, 1.47mmol, 2.5 equiv) was added. The mixture was then cooled to -5 °C and N-ethylmorpholine was added under nitrogen. The reaction mixture was stirred overnight at room temperature. The mixture was concentrated and the residue taken up with CH_2Cl_2 (20ml), cold H_2O (20ml), 1M HCl (20ml). After decantation, the aq. phase was reextracted with CH_2Cl_2 (2 x 20ml). The combined organic phase was washed with 10% $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. The resulting oil was purified on silica gel (1% methanol in CH_2Cl_2) affording the bicyclic compound (**254**) as a solid (65mg, 25%): $[\alpha]_D^{20}$ -77 (c 0.208, MeOH); IR (KBr) 3471, 3434, 2975, 2928, 1767, 1723, 1443, 1389, 1284, 1243, 1151, 1112, 720; ^1H NMR ($CDCl_3$)

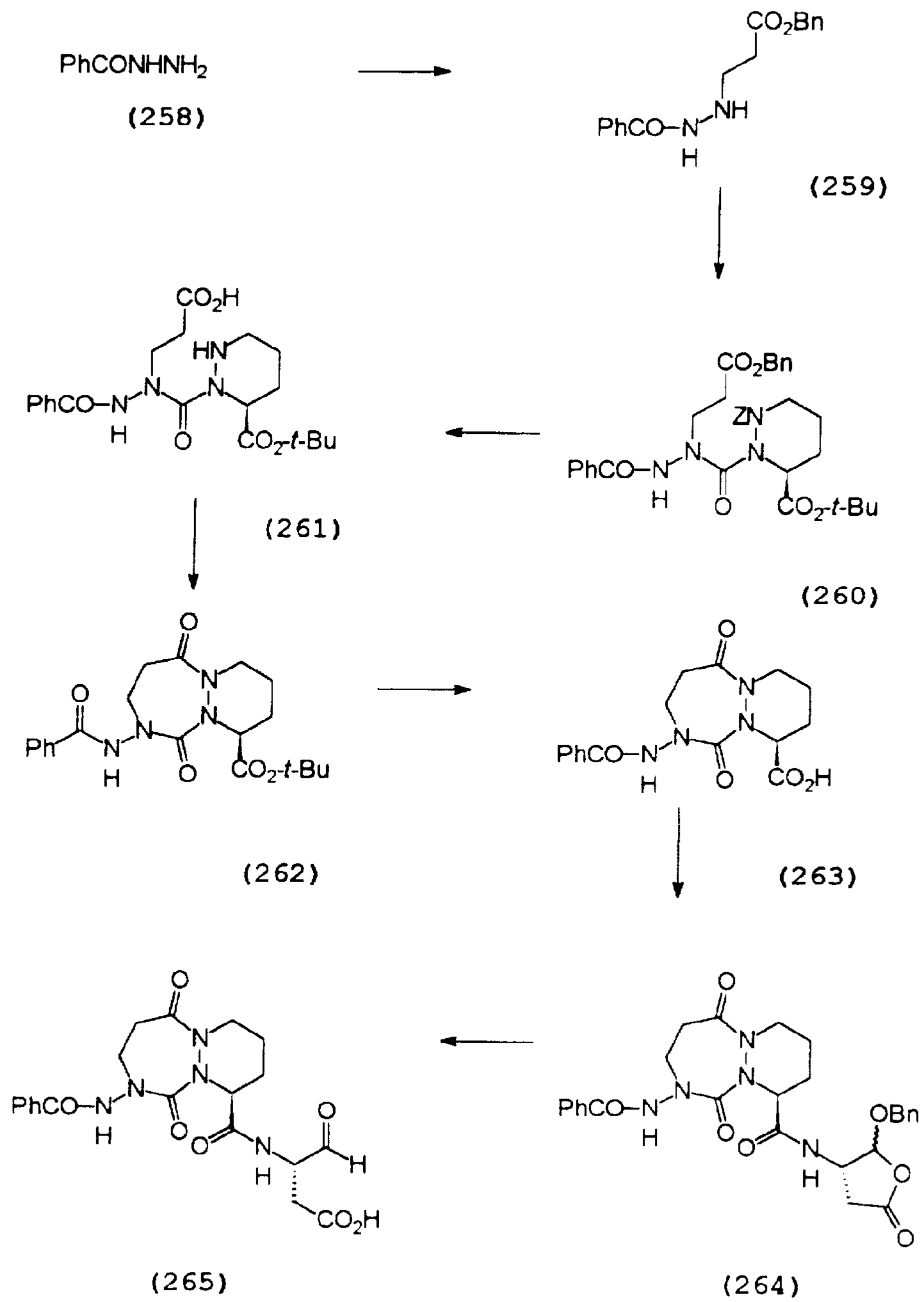
δ 7.94-7.69 (4H, m), 5.34-5.27 (1H, m), 4.89-4.66 (2H, m), 3.94-3.64 (2H, m), 3.02-2.84 (1H, m), 2.34-2.19 (2H, m), 1.94-1.61 (3H, m), 1.47 (9H, s), 1.14 (3H, d); Anal. Calcd for $C_{23}H_{27}N_3O_6$: C, 62.57; H, 6.17; N, 9.52. Found: C, 62.60; H, 6.40; N, 9.10.

(1*S*, 8*S*, 9*S*) t-Butyl-9-benzoylamino-6,10-dioxo-8-methyl-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (255). A solution of the bicyclic compound (**254**) (70mg, 0.16mmol) in ethanol was treated with hydrazine hydrate (0.02ml, 4mmol, 2.5 equiv). After 5h stirring at room temperature, the mixture was concentrated and the resulting residue taken up in toluene and reevaporated. The residue was treated with 2M acetic acid (2ml) for 16h. The resulting precipitate was filtered and washed with 2M acetic acid (10ml). The filtrate was basified with solid $NaHCO_3$ and then extracted with EtOAc. The organic solution was washed with water, dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (2% methanol in CH_2Cl_2) afforded the free amine as a foam (50mg, 100%). The amine (50mg, 0.16mmol) was dissolved in dioxane (1ml) and water (0.25ml) and treated with $NaHCO_3$ (0.034g, 0.04mmol) followed by benzoylchloride (0.047ml, 0.40mmol, 2.8 equiv). The mixture was stirred overnight at room temperature, then diluted with EtOAc (15ml). The organic solution was washed with 10% $NaHCO_3$ and sat. aq. NaCl, dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (2% methanol in CH_2Cl_2) afforded the benzamide **255** as a foam (67mg, 100%): ^1H NMR ($CDCl_3$) δ 7.89-7.39 (5H, m), 6.79 (1H, d), 5.32-5.20 (1H, m), 4.98-4.82 (1H, m), 4.75-4.64

(1H, m), 3.84-3.65 (1H, m), 3.09-2.89 (1H, m), 2.45-2.18 (2H, m), 2.00-1.61 (4H, m), 1.48 (9H, s), 1.28 (3H, d).

[3*S*(1*S*, 8*S*, 9*S*)] 3-(9-benzoylamino-6,10-dioxo-8-methyl-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (257). A solution of t-butyl ester **255** (67mg, 0.16mmol) in CH_2Cl_2 (1ml) was treated at 0 °C with trifluoroacetic acid (1ml). The resulting solution was stirred at 0 °C for 15min and then at room temperature for 1h. The solution was concentrated, the residue taken up in dry CH_2Cl_2 (2 x 2ml) and the mixture again concentrated (x2). The residue was crystallized from diethylether. Filtration of the precipitate afforded the free acid of **255** as a grey solid (40mg, 70%). A solution of acid (40mg, 0.11mmol), N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett., 2, pp. 615-18 (1992); 39mg, 0.13mmol, 1.2equiv) and $(Ph_3P)_2PdCl_2$ (3mg) in a mixture of dry CH_2Cl_2 (1ml) and dry DMF (0.2ml) was treated dropwise with n-Bu_3SnH (0.089ml, 0.33mmol, 3 equiv). The resulting solution was stirred at 25 °C for 10min and then 1-hydroxybenzotriazole (36mg, 0.266mmol, 2.4 equiv) was added. The mixture was cooled to 0 °C and ethyldimethylaminopropyl carbodiimide (31mg, 0.16mmol, 1.5equiv) was added. After stirring at 0 °C for 10min and then at room temperature overnight, the mixture was diluted with EtOAc (20ml) and the resulting solution washed successively with 1M HCl (2 x 5ml), 10% $NaHCO_3$ (2 x 5ml) and sat. aq. NaCl (5ml), dried ($MgSO_4$) and concentrated. Flash chromatography on silica gel (2% methanol in CH_2Cl_2) afforded a mixture of

diastereoisomers (**256**) as a grey solid (50mg, 82%). This product (**256**) was used without further purification (50mg, 0.091mmol) and was hydrogenated in methanol (5ml) using 10% Pd/carbon (30mg) for 24h. The reaction mixture was filtered and the resulting solution concentrated. Flash chromatography on silica gel (2-20% methanol in CH_2Cl_2) afforded compound **257** (9mg, 21%) as a white solid: ^1H NMR (D^4-MeOH) δ 7.88-7.29 (5H, m), 5.18-4.99 (1H, m), 4.59-4.35 (3H, m), 4.26-4.11 (1H, m), 3.65-3.41 (2H, m), 3.18-2.91 (1H, m), 2.62-1.47 (8H, m), 1.29-1.00 (3H, 2d) (mixture of acetal and hemiacetal). MS (ES -) 457.



Benzyl 3-(N'-benzoylhydrazino)propanoate (259). Benzylacrylate (1.13ml, 7.34mmol) was added to a stirred suspension of benzoylhydrazine (**285**) (1.0g, 7.34mmol) in isopropanol (28ml). The mixture was

refluxed for 20h, cooled to room temperature then concentrated. The residue was purified by flash chromatography (20% EtOAc in CH_2Cl_2) to afford **259** (1.098g, 50%) as an oil which crystallized on standing: mp 65 °C; IR (KBr) 3283, 1723, 1644, 1316, 1201, 1156; ^1H NMR ($CDCl_3$) δ 8.32-8.18 (1H, m), 7.81-7.70 (2H, m), 7.57-7.23 (8H, m), 5.36-4.92 (1H, brm), 5.11 (2H, s), 3.26 (2H, t, J = 6.5), 2.59 (2H, t, J = 6.5); ^{13}C NMR ($CDCl_3$) δ 172.12, 167.27, 135.65, 132.54, 131.66, 128.45, 128.10, 128.06, 126.84, 66.31, 47.33, 33.31; Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.42; H, 6.10; N, 9.38. MS (ES +) 321 (M + Na, 38%), 299 (M^+ + 1, 100).

(3*S*)-1-Benzyl 3-t-butyl 2-(N'-benzoyl-N-(2-benzyloxycarbonylethyl)hydrazinocarbonyl)hexahydropyridazine-1,3-dicarboxylate (260). A solution of (3*S*)-1-benzyl 3-t-butyl hexahydropyridazine-1,3-dicarboxylate (Hassall et al. <u>J. Chem. Soc. Perkin 1</u>, pp. 1451-1454 (1979)) (925.3mg, 2.89mmol) and diisopropylethylamine (0.70ml, 4.0mmol) in a 1.93M toluene solution of phosgene (17.96ml, 34.7mmol) was stirred at room temperature for 45min, then concentrated to leave a yellow solid. To this solid was added toluene (18ml), hydrazide (**259**) (861.6mg, 2.89mmol) and diisopropylethylamine (0.70ml, 4.0mmol). The mixture was stirred at room temperature for 2.75h, then concentrated. The resulting residue was taken up in EtOAc, washed twice with 1M HCl, brine, then dried ($MgSO_4$), filtered and concentrated to afford 2.15g of crude material. Flash chromatography (40% EtOAc in hexane) afforded 1.65g (89%) of the title compound as a white foam: mp 40 °C; $[\alpha]_D24$ -55.78 ° (c 0.40, CH_2Cl_2);

IR (KBr) 3436, 2930, 1733, 1689, 1455, 1412' 1367, 1258, 1156, 697; ^1H NMR ($CDCl_3$) δ 8.54-8.23 (0.5H, m), 7.97-7.09 (15.5H), 5.16-4.80 (4H, m), 4.66-4.32 (1H, m), 4.24-3.55 (3.3H, m), 3.50-3.26 (0.4H, m), 3.19-2.49 (2.3H, m), 2.11-1.43 (6H, m), 1.32-1.05 (7H, m); Anal. Calcd for $C_{35}H_{40}N_4O_8 \cdot 0.5H_2O$: C, 64.31; H, 6.32; N, 8.57. Found: C, 64.18; H, 6.27; N, 8.56. MS (ES +) 662 (M + Na, 84%), 645 (M^+ + 1, 100), 384 (77).

(6*S*)-3-(N'benzoyl-N-(6-t-butoxycarbonylhexahydropyridazine-1-carbonyl)hydrazino)propanoic acid (261). A solution of **260** (1.59g, 2.47mmol) in MeOH (142ml) was treated with 10% Palladium on carbon (230.0mg) and stirred under an atmosphere of H_2 for 1.5h. The mixture was filtered and the solvent evaporated to afford 1.04g (100%) of a white foam. This was used in the next step without further purification: mp <40 °C; $[\alpha]_D^{26}$ +1.6 ° (c 0.26, CH_2Cl_2); IR (KBr) 3422, 2977, 2986, 1728, 1677, 1486, 1445, 1396, 1369, 1309, 1228, 1155, 916, 716; ^1H NMR ($CDCl_3$) δ 10.0-9.7 (1H, brm), 7.86 (2H, d, *J* = 7.5), 7.62-7.38 (3H, m), 7.3-5.6 (2H, brm), 4.57 (1H, brd, *J* = 4.0), 4.05-3.77 (2H, m), 3.00-2.82 (1H, m), 2.80-2.43 (3H, m), 2.20-2.03 (1H, m), 2.00-1.47 (1H, m), 1.62-1.14 (11H, m); ^{13}C NMR ($CDCl_3$) δ 175.00, 171.17, 167.62, 160.68, 132.39, 131.77, 128.67, 127.38, 82.27, 54.38, 48.04, 46.35, 33.62, 28.02, 25.68, 21.61. MS (ES +) 443 (M + Na, 68%), 421 (M^+ + 1), 100), 365 (50), 131 (61).

(4*S*) t-Butyl 7-benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262). To a solution of amino acid **261**

(1.012g, 2.41mmol) in dry THF (26ml) at 0 °C was added N-ethylmorpholine (597µl, 4.69mmol), followed by PCl_5 (651.3mg, 3.12mmol). The reaction was stirred at 0 °C for 2h, then allowed to warm to rt and stirred for a further 15.5h. The mixture was concentrated and the resulting residue taken up in EtOAc, washed twice with 1M HCl, sat. $NaHCO_3$, brine, then dried ($MgSO_4$), filtered and concentrated. Flash chromatography (20% EtOAc in CH_2Cl_2) gave 727.3mg (75%) of the title compound as a white foam: $[\alpha]_D^{26}$ +51.0 ° (c 0.20, CH_2Cl_2); IR (KBr) 3436, 2979, 1733, 1670, 1483, 1437, 1420, 1299, 1243, 1156; ^1H NMR ($CDCl_3$) δ 8.70 (1H, s), 7.78 (2H, d, *J* = 7.0), 7.57-7.32 (3H, m), 5.08 (1H, dd, *J* = 2.5, 5.5), 4.59-4.43 (1H, m), 4.08-3.69 (3H, m), 3.07-2.84 (1H, m), 2.57-2.35 (1H, m), 2.34-2.14 (1H, m), 2.07-1.43 (3H, m), 1.48 (9H, s); ^{13}C NMR ($CDCl_3$) δ 172.41, 169.04, 166.35, 158.35, 132.24, 132.03, 128.61, 127.31, 82.77, 55.41, 54.07, 41.57, 32.21, 28.04, 24.97, 20.37; Anal. Calcd for $C_{20}H_{26}N_4O_5$: C, 59.69; H, 6.51; N, 13.92. Found: C, 59.53; H, 6.53; N, 13.84. MS (ES +) 425 (M + Na, 71%), 403 (M^+ + 1, 100), 145 (41).

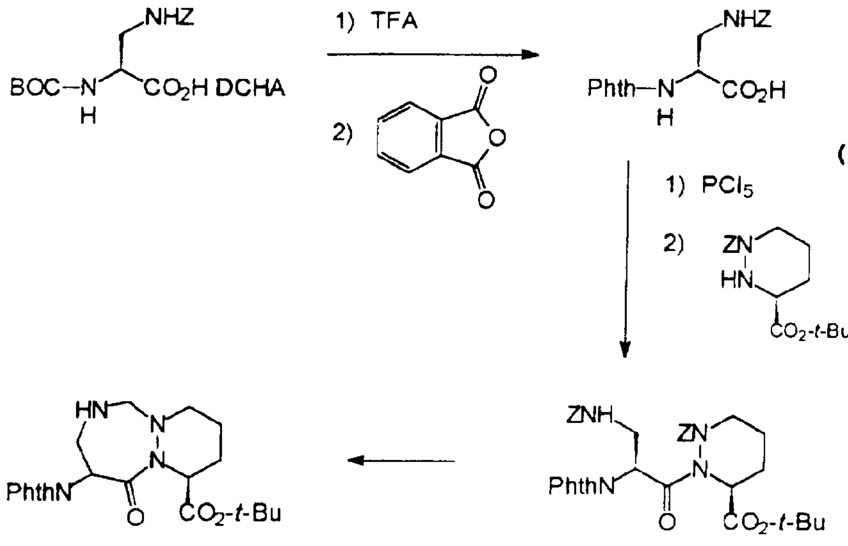
(4*S*)-7-Benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic Acid (263). A solution of ester **262** (720.0mg, 1.80mmol) in a 1:1 mixture of CH_2Cl_2 and TFA (150ml) was stirred for 1.3h under a dry atmosphere. The solution was then reduced *in vacuo*, taken up in Et_2O and reduced again. This process was repeated six times to afford the crude product as an off-white solid. The product was purified by flash chromatography (5% MeOH in CH_2Cl_2) to afford 520.0mg (83%) of the title compound as a white

foam: $[\alpha]_D^{25}$ +59.5 ° (c 1.82, CH_2Cl_2); IR (KBr) 3435, 3266, 2956, 1732, 1664, 1524, 1486, 1440, 1302; ^1H NMR ($CDCl_3$) δ 9.13 (1H, s), 7.77 (2H, d, J = 7.5), 7.57-7.32 (3H, m), 5.27-5.16 (1H, m), 4.62-4.43 (1H, m), 4.09-2.70 (3H, m), 3.14-2.89 (1H, m), 2.59-2.43 (1H, m), 2.38-2.20 (1H, m), 2.14-1.89 (1H, m), 1.82-1.59 (2H, m); ^{13}C NMR ($CDCl_3$) δ 173.65, 172.28, 166.44, 158.42, 132.44, 131.31, 128.61, 127.39, 54.83, 54.01, 42.11, 31.79, 24.42, 20.29; MS (ES -) 345 (M - H^+, 100%), 161 (45).

[2*RS*,3*S*(4*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264). To a solution of acid **263** (300.0mg, 0.87mmol) and (2*RS*,3*S*)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett. 2, pp. 615-18 (1992)) (277.6mg, 0.95mmol) in dry CH_2Cl_2 (2.5ml) and dry DMF (2.5ml) at rt was added bis(triphenylphosphine) palladium chloride (13.0mg), followed by tri-n-butyltin hydride (466.0µl, 1.73mmol). The reaction was stirred for 5min, then 1-hydroxybenzotriazole (234.1mg, 1.73mmol) was added and the mixture was cooled to 0 °C before addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (204.5mg, 1.04mmol). The mixture was allowed to warm to rt and stirred for 16.5h. The mixture was diluted with EtOAc, washed with 1M $NaHSO_4$ twice with sat. $NaHCO_3$, then H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (5% MeOH in CH_2Cl_2) to afford 358.3mg (77%) of the title compound as a white solid: IR (KBr) 3435, 1791, 1665, 1526,

1421, 1285; ^{1}H NMR ($CDCl_3$) δ 8.76 and 8.49 (1H, 2 x s), 7.92-7.73 (2H, m), 7.62-7.24 (8.5H, m), 6.86 (0.5H, d, J = 8.0), 5.53 and 5.33 (1H, d, J = 5.5, s), 4.95-4.34 (5H, m), 4.04-3.54 (3H, m), 3.03-2.64 (2H, m), 2.49-2.14 (2H, m), 2.11-1.46 (4H, m); MS (ES +) 558 (M + Na, 100%), 536 (M^+ + 1, 78), 404 (58).

[3*S*(4*S*)]3-(7-Benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (265). A mixture of **264** (350.0mg, 0.65mmol), 10% palladium on carbon (350mg) and methanol (36ml) was stirred under an atmosphere of H_2 for 6.5h. The mixture was filtered and the solvent evaporated. Et_2O was added and the solvent removed again. This process was repeated four times to reveal 283mg (97%) of the title compound, as a white crystalline solid: mp decarboxylates above 140 °C; $[\alpha]_D^{26}$ +33.5 ° (c 0.18, MeOH), IR (KBr) 3428, 1663, 1528, 1487, 1437, 1288; ^{1}H NMR (D_6-DMSO) δ 10.56 (1H, s), 8.71-8.57 (1H, m), 7.88-7.81 (2H, m), 7.65-7.46 (3H, m), 4.97-4.85 (1H, m), 4.38-4.0 (3H, m), 3.88-3.52 (3H, m), 2.91-2.71 (2H, m), 2.50-2.38 (1H, m), 2.35-2.21 (1H, m), 2.10-1.94 (1H, m), 1.93-1.49 (3H, m); ^{13}C NMR (D_6-DMSO) δ 173.66, 172.49, 169.97, 169.89, 164.96, 157.62, 132.35, 131.85, 128.39, 127.32, 53.81, 52.69, 40.90, 33.17, 31.60, 24.40, 24.13, 19.24; MS (ES -).



(266)

(268) (267)

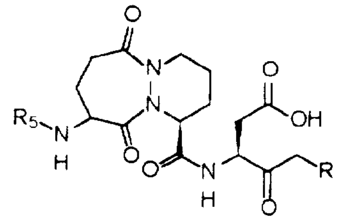
(2*S*) 3-Benzyloxycarbonylamino-2-phthalimidopropionic acid (266). A solution of (2S) 3-benzyloxycarbonylamino-2-tert-butoxycarbonylaminopropionic acid dicyclohexylamine salt (3g, 5.8mmol) in dichloromethane (200ml) was washed four times with 1M HCl solution, dried ($MgSO_4$) and concentrated. The resulting oil was dissolved in dry dichloromethane (35ml), cooled to 0 °C and treated with trifluoroacetic acid (35ml). This solution was stirred at 0 °C for 1.5h then evaporated to dryness. Dichloromethane (50ml) was added to the residue then removed under vacuum. This process repeated six times to afford a white solid. The white solid was suspended in toluene (50ml), treated with powdered phthalic anhydride (940mg, 6.35mmol) and refluxed for 18h. The resulting solution was concentrated to afford an oil which was purified by flash chromatography (2-10% methanol/dichloromethane) to afford **266**, 2.01g (94%) as a white powder: IR (KBr) 3600-2500br, 1776, 1714,

1530, 1469, 1455, 1392, 1263, 1131, 722; ^{1}H NMR ($CDCl_3$) δ 7.83 (2H, m), 7.72 (2H, m), 7.29 (5H, m), 5.41 (1H, m), 5.03 (2H, s), 3.90 (2H, m); MS (ES-), 367 (M - 1).

[3*S* (2*S*)] t-Butyl 1-benzyloxycarbonyl-2-(3-benzyloxycarbonylamino-2-phthalimidopropionyl)pyridazine-3-carboxylate (267). A suspension of the acid **266** (1.32g, 3.58mmol) in dry ether (37ml) was treated with phosphorus pentachloride (1.04g, 5mmol) and stirred at room temperature for 2h. The solution was filtered to remove unreacted phosphorus pentachloride then evaporated to dryness. The residue was treated with dry toluene (25ml) then evaporated to dryness. This process was repeated several times. The resulting oil was dissolved in dry dichloromethane (25ml), cooled to 0 °C and treated with a solution of (3*S*) t-butyl 1-benzyloxycarbonylpyridazine-3-carboxylate (1.15g, 3.58mmol) in dry dichloromethane (2ml) followed by 5% aqueous sodium bicarbonate solution (25ml). The mixture was stirred rapidly at room temperature for 20h then diluted with ethyl acetate (100ml) and acidified to pH2 with 1M HCl. The organic phase was washed twice with dilute HCl solution then brine, dried ($MgSO_4$) and concentrated. The resulting oil was purified by flash chromatography (2-20% ethyl acetate/dichloromethane then 10-20% methanol/dichloromethane) to afford (**267**), 1.25g (52%) as a white powder: IR (KBr) 3367, 2955, 1722, 1517, 1455, 1387, 1369, 1251, 1153, 721; ^{1}HÊNMR ($CDCl_3$) δ 7.81 (2H, m), 7.74 (2H, m), 7.63 (1H, brs), 7.31 (10H, m), 5.46-4.76 (5H, m), 4.07-3.54 (4H, m), 2.4 (1H, m), 2.0-1.6 (3H, m), 1.40 (9H, s); MS (ES+), 671 (M + 1), 693 (M + Na).

(1*S*,9*S*) t-Butyl 1,2,3,4,7,8,9,10-octahydro-10-oxo-9-phthalimido-6H-pyridazino[1,2-a][1,2,4]triazepine-1-carboxylate (268). A solution of ester **267** (50mg, 0.074mmol) in methanol (15ml) was treated with 10% palladium on carbon (50mg) and hydrogenated at room temperature and atmospheric pressure for 24h. The mixture was evacuated thoroughly to remove hydrogen then treated with 37% aqueous formaldehyde (18mg, 0.22mmol) and stirred under nitrogen for 2h. The mixture was filtered, evaporated to dryness and the product purified by flash chromatography (4-100% ethyl acetate/dichloromethane) to afford **268** 14.5mg (48%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.85 (2H, m), 7.71 (2H, m), 5.78 (1H, dd, J = 10, 5), 4.99 (1H, dd, J = 6.1, 1.5), 4.07 (1H, d, J = 10.6), 3.49 (1H, dd, J = 14, 5), 3.39 (1H, d, J = 10.3), 3.24 (1H, dd, J = 14, 10.2), 3.17 (2H, m), 2.39 (1H, m), 1.84-1.46 (3H), 1.51 (9H, s); MS (ES+), 415 (M + 1), 437 (M + Na).

Compounds **280-283** were prepared from **212b** by a method similar to the method used to prepare **226e**. Compounds **284-287** were prepared by a method similar to the method used to prepare **217e**.



280-287

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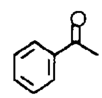
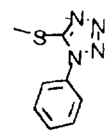
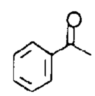
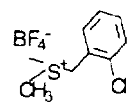
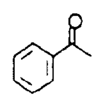
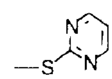
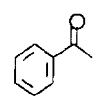
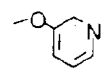
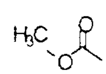
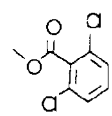
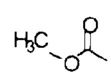
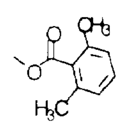
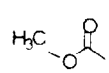
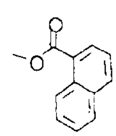
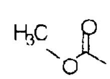
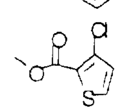
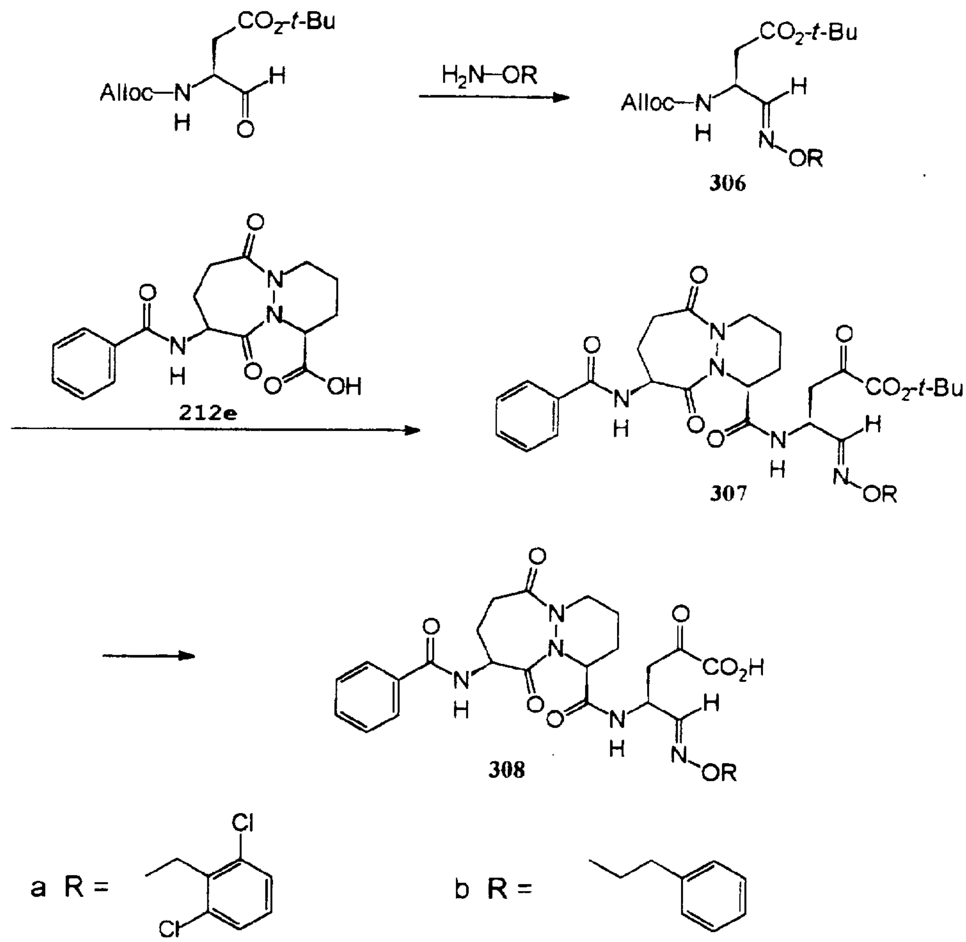
280		
281		
282		
283		
284		
285		
286		
287		



(3*S*) 3-Allyloxycarbonylamino-4-oxobutyric acid tert-butyl ester O-(2,6-dichlorophenylmethyl)oxime (306a) was prepared by a similar procedure as **208a** except that 2,6-dichlorophenylmethoxyamine (prepared by a similar method as **306b**) was used instead of semicarbazide to give 870mg (quant.) as a clear oil.

(3*S*) 3-Allyloxycarbonylamino-4-oxobutyric acid tert-butyl ester O-(2-(phenyl)ethyl)oxime (306b) was prepared by a similar procedure as **208a** except that 2-

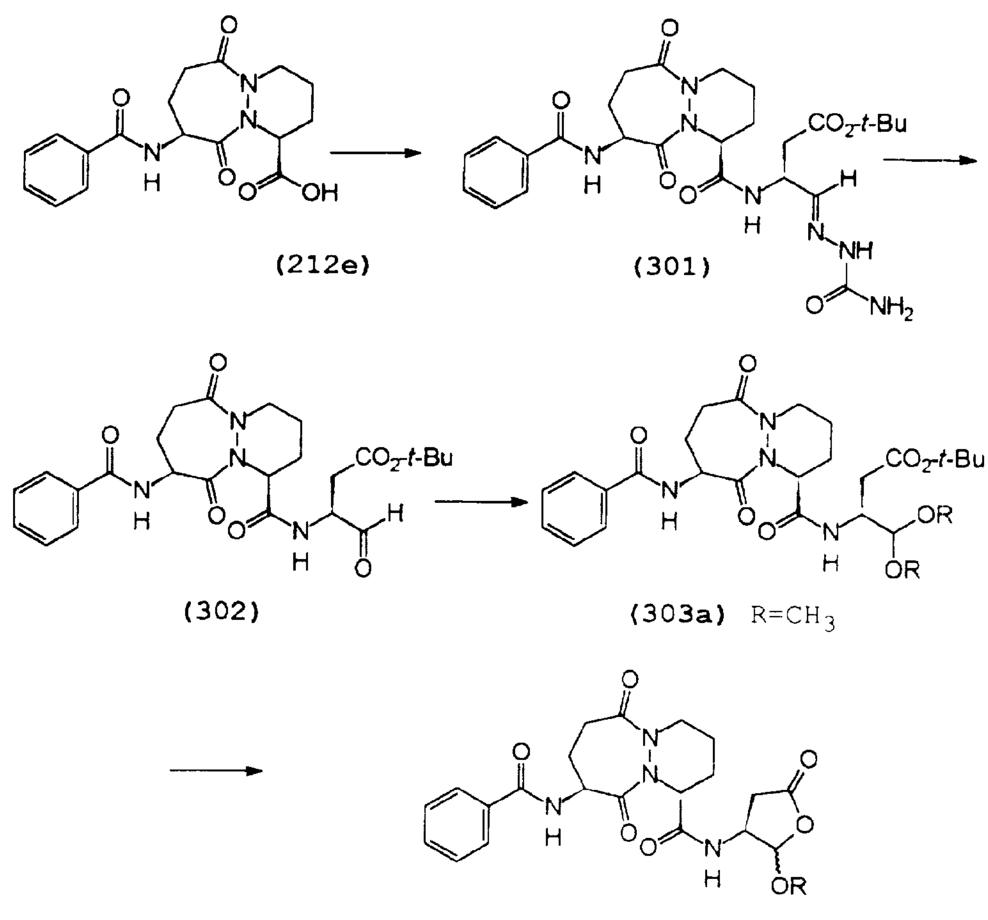
(phenyl)ethoxyamine (US 5 346 911) was used instead of semicarbazide to give 395mg (quant.) as a clear oil.

[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoicacid t-butyl ester, O-(2,6-dichlorophenylmethyl)oxime (307a) was prepared by a procedure similar to **233e** except **306a** was used instead of **207a** to give 23 mg(23%) of **307a** as a white solid.

[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid t-butyl ester, O-(2-(phenyl)ethyl)oxime (307b) was prepared by a procedure similar to **233e** except **306b** was used instead of **207a** to give 43 mg(48%) of **307b** as a white solid.

[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid, O-(2,6-dichlorophenylmethyl)oxime (308a) was prepared by from **307a** a procedure similar to the preparation of **235e** from **234e** to give 15.2 mg (74%) as white solid: ^1H NMR(CD_3OD) δ 0.9(m), 1.3(s), 1.7(m), 1.8(m), 2.0(m), 2.1-2.2(m), 2.3(dd), 2.4-2.5(m), 2.6(m), 2.7-2.8(m), 3.1(m), 3.3(m), 3.4-3.5(m), 4.5(m), 4.9(m), 5.1(m), 5.3(d), 5.4(s), 6.8(d), 7.2-7.5(m), 7.8(dd), 8.4(dd).

[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid, O-(2-(phenyl)ethyl)oxime (308b) was prepared by from **307b** a procedure similar to the preparation of **235e** from **234e** to give 25.2 mg (68%) as white solid: ^{1}H NMR(CD_3OD) δ 1.2(m), 1.6-1.7(m), 2.0-2.1(m), 2.2(m), 2.3(m), 2.5(m), 2.6-2.7(dd), 2.9(t), 3.0(t), 3.1(m), 3.3-3.5(m), 4.2(t), 4.25(m), 4.5(m), 5.2(t), 5.3(t), 6.7(d), 7.1-7.2(m), 7.35(dd), 7.4(m), 7.5(m), 7.8(dd), 8.3(dd).



(212e) **(301)** **(302)** **(303a)** R=CH_3 **(304a)** R=CH_3

[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyriazino-[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid tert-butyl ester (302).

Step A: **301** was prepared by procedure similar to **605a** (Step A), except **212e** was used instead of **603a** to give 540 mg (34%) to give a white solid.

Step B: **302**. A solution of **301** (50.7 mg; 0.091 mmol) in 2.8 ml of MeOH/HOAc/37% aq. formaldehyde (5:1:1) was stirred at rt for 5.5 h. and the reaction was concentrated to 0.7 ml *in vacuo*. The residue was dissolved in 3 ml of CH_3CN and concentrated to 0.7 ml (3x), dissolved in toluene and concentrated to 0.7 ml *in vacuo* (2x), and concentrated to dryness. Chromatography (flash, SiO_2, 5% isopropanol/CH_2Cl_2) gave **302** (45.5 mg, 78%) as a white solid: ^1H NMR(DMSO-d_6) δ 1.0-1.15(m, 2H), 1.4(s, 9H), 1.65(m, 2H), 1.9-2.1(m, 2H), 2.15-2.4(m, 3H), 2.55(m, 1H), 2.7-3.0(m, 2H), 4.3-4.6(m, 2H), 4.9(m, 1H), 5.2(m, 1H), 7.4-7.6(m, 2H), 7.8-8.0(m, 2H), 8.6(m, 1H), 8.8(m,1H), 9.4(s, 1H).

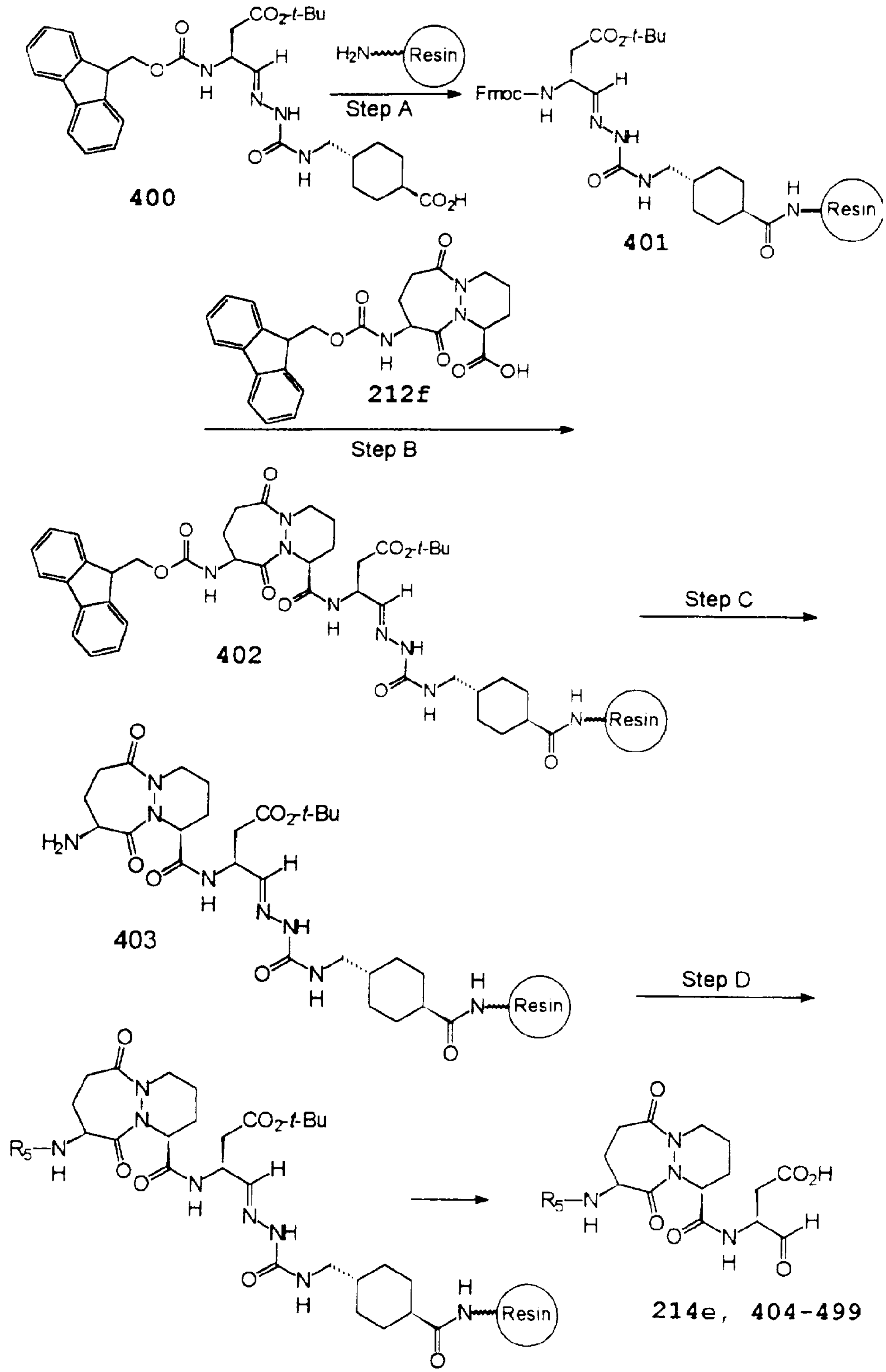
[1*S*,9*S* (2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-methoxy-5-oxo-tetrahydro-furan-3-yl)-6H-pyridazino[1,2-a][1,2]diazapine-1-carboxamide. (304a).

Step A: A solution of **302** (90 mg; 0.18 mmol) in 10 ml of MeOH was treated with trimethylorthoformate (1ml) and p-toluene sulfonic acid hydrate (5 mg; 0.026 mmol) and the reaction was stirred for 20 h. The reaction was treated with 3 ml of aq. sat. $NaHCO_3$ and concentrated *in vacuo*. The residue was taken up in

EtOAc and washed with dilute aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo* to give 80 mg of **303a**. **Step B**: **303a** was dissolved in 2 ml of TFA and stirred at rt for 15 min. The reaction was dissolved in CH_2Cl_2 and concentrated *in vacuo* (3x). Chromatography (flash, SiO_2, 1% to 3% $MeOH/CH_2Cl_2$ gave 43 mg (64%) of **304a** as a white solid: ^1H NMR($CDCl_3$) δ 1.55-1.8(m, 2H), 1.9-2.15(m, 4H), 2.25-2.5(m, 2H), 2.7-3.3(m, 4H), 3.45, 3.6(s, s, 3H), 4.4, 4.75(2m, 1H), 4.6(m, 1H), 4.95, 5.4(t,d, 1H), 5.1-5.2(m, 1H), 6.45, 7.05(2d, 1H), 6.95(m, 1H), 7.45(m, 2H), 7.5(m, 1H), 7.85(m, 2H).

Example 11

Compounds **214e**, **404-413**, **415-445**, **446-468**, **470-491**, and **493-499** were synthesized as described in Example 11 and Table 7.


Step A
400
401
212f
Step B
402
Step C
403
Step D
214e, 404-499

Step A. Synthesis of 401. TentaGel S® NH_2 resin (0.16 mmol/g, 10.0 g) was placed in a sintered glass funnel and washed with DMF (3 x 50 mL), 10% (v/v) DIEA in DMF (2 x 50 mL) and finally with DMF (4 x 50 mL). Sufficient DMF was added to the resin to obtain a slurry followed by **400** (1.42 g, 2.4 mmol, prepared from (3*S*)-3-(fluorenylmethyloxycarbonyl)-4-oxobutryic acid *t*-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), 1-hydroxybenzotriazole hydrate (HOBT•H_2O; 0.367 g, 2.4 mmol), *O*-benzotriazol-1-yl-*N,N,N,N'*-tetramethyluronium hexafluorophosphate (HBTU; 0.91 g, 2.4 mmol), and DIEA (0.55 mL, 3.2 mmol). The reaction mixture was agitated overnight at rt using a wrist arm shaker. The resin was isolated on a sintered glass funnel by suction filtration and washed with DMF (3 x 50 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) Ac_2O/DMF (2 x 25 mL) directly in the funnel (10 min/wash). The resin was washed with DMF (3 x 50 mL) and CH_2Cl_2 (3 x 50 mL) prior to drying overnight *in vacuo* to yield **401** (11.0 g, quantitative yield).

Step B. Synthesis of 402. Resin **401** (6.0 g, 0.16 mmol/g, 0.96 mmol) was swelled in a sintered glass funnel by washing with DMF (3 x 25 mL). The Fmoc protecting group was then cleaved with 25% (v/v) piperidine/DMF (25 mL) for 10 min (intermittent stirring) and then for 20 min with fresh piperidine reagent (25 ml). The resin was then washed with DMF (3 x 25 ml), followed by *N*-methypyrrolidone (2 x 25 mL). After transferring the resin to a 100 mL flask, *N*-methypyrrolidone was added to obtain a slurry followed

by **212f** (0.725 g, 1.57 mmol), HOBT•H_2O (0.25 g, 1.6 mmol), HBTU (0.61 g, 1.6 mmol) and DIEA (0.84 mL, 4.8 mmol). The reaction mixture was agitated overnight at rt using a wrist arm shaker. The resin work-up and capping with 20% (v/v) Ac_2O in DMF were performed as described for **401** to yield **402** (6.21 g, quantitative yield).

Step C. Synthesis of 403. This compound was prepared from resin **402** (0.24 g, 0.038 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with DMF (3 x 1 mL), deprotection with 25% (v/v) piperidine in DMF (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **403**. The resin was washed with DMF (3 x 1 mL) and *N*-methypyrrolidone (3 x 1 mL).

Step D. Method 1. [3*S*(1*S*,9*S*)]-3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(thiophene-3-carbonylamino)-6*H*-pyridazine[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (409). Resin **403** was acylated with a solution of 0.4M thiophene-3-carboxylic acid and 0.4M HOBT in *N*-methypyrrolidone (1 mL), a solution of 0.4M HBTU in *N*-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) and the reaction was shaken for 2 hr at rt. The acylation step was repeated. Finally, the resin was washed with DMF (3 x 1 mL), CH_2Cl_2 (3 x 1 mL) and dried *in vacuo*. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/5% H_2O (v/v, 1.5 mL) for 30 min at rt. After washing the resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 Et_2O:pentane (12 mL)

and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% CH_3CN/90% H_2O/0.1% TFA (15 mL) and lyophilized to obtain crude **409** as a white powder. The compound was purified by semi-prep RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 x 250 mm) eluting with a linear CH_3CN gradient (5% - 45%) containing 0.1% TFA (v/v) over 45 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **409** (10.8 mg, 63%).

Step D. Method 1A. Synthesis of 418. Following a similar procedure as method 1, resin **403** was acylated with 4-(1-fluorenylmethoxycarbonylamino)benzoic acid and repeated. The Fmoc group was removed as described in Step C and the free amine was acetylated with 20% (v/v) Ac_2O in DMF (1 mL) and 1.6M DIEA in *N*-methylpyrrolidone (0.35 mL) for 2 hr at rt. The acetylation step was repeated. Cleavage of the aldehyde from the resin gave **418** (3.2 mg).

Step D. Method 1B. Synthesis of 447. Following a similar procedure as method 1A, resin **403** was acylated with 0.4M 4-(1-fluorenylmethoxycarbonylamino)benzoic acid. The acylation step was repeated once. The Fmoc group was removed as before and the free amine was reacted with 1M methanesulfonyl chloride in CH_2Cl_2 (0.5 mL) and 1M pyridine in CH_2Cl_2 (0.60 mL) for 4 hr at rt. Cleavage of the aldehyde from the resin gave **447** (10.0 mg).

Step D. Method 2. Synthesis of 214e. Following a similar procedure as method 1, resin **403** was acylated

with 0.5M benzoyl chloride in *N*-methypyrrolidone (1 mL) and 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) for 2 hr at rt. The acylation step was repeated. Cleavage of the aldehyde from the resin gave **214e** (5.1 mg, 30%).

Step D. Method 3. Synthesis of 427. Following a similar procedure as method 1, resin **403** was reacted with 1.0M benzenesulfonyl chloride in CH_2Cl_2 (0.5 mL) and 1M pyridine in CH_2Cl_2 (0.60 mL) for 4 hr at rt. The reaction was repeated. Cleavage of the aldehyde from the resin gave **427** (7.2 mg, 40%).

Step D. Method 4. Synthesis of 420. Following a similar procedure as method 1, resin **403** was reacted with 0.5M methylisocyanate in *N*-methypyrrolidone (1 mL) and 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) for 2 hr at rt. The reaction was repeated. Cleavage of the aldehyde from the resin gave **420** (8.3 mg, 55%).

Step D. Method 5. Synthesis of 445. Following a similar procedure at method 1, resin **403** was acylated with 0.27M imidazole-2-carboxylic acid (1 mL) in 2:1 DMF:H_2O (with 1 eq. DIEA) and 1M 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in 2:1 *N*-methypyrrolidone/H_2O (0.35 mL) for 3 hr at rt. Cleavage of the aldehyde from the resin gave **445** (9.5 mg).

Analytical HPLC methods:

(1) Waters DeltaPak C18, 300A (5μ, 3.9 x 150 mm). Linear CH_3CN gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

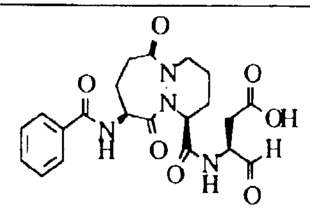
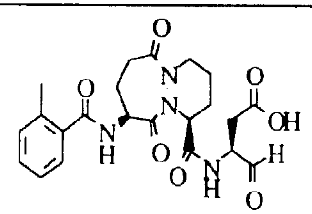
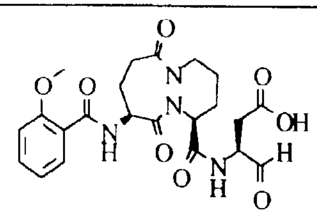
(2) Waters DeltaPak C18, 300A (5µ, 3.9 x 150 mm). Linear CH_3CN gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

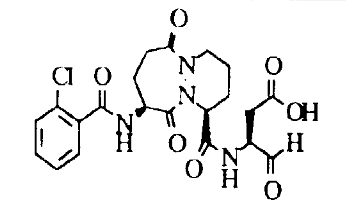
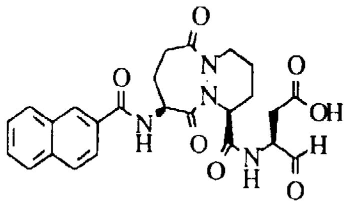
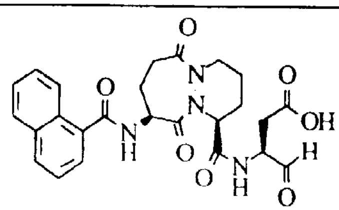
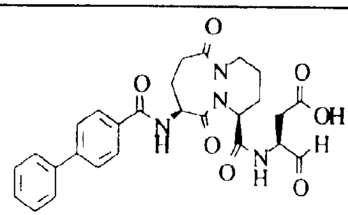
(3) Waters DeltaPak C18, 300A (5µ, 3.9 x 150 mm). Isocratic elution with 0.1% TFA/water (v/v) at 1 mL/min.

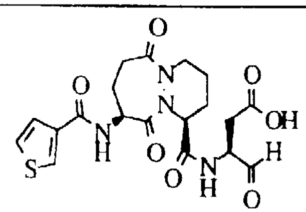
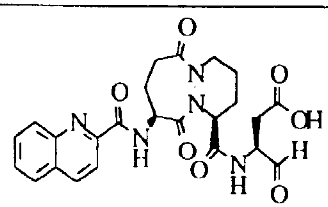
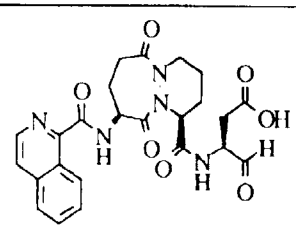
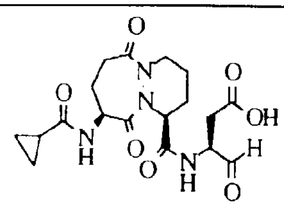
(4) Waters DeltaPak C18, 300A (5µ, 3.9 x 150 mm). Linear CH_3CN gradient (0% - 30%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

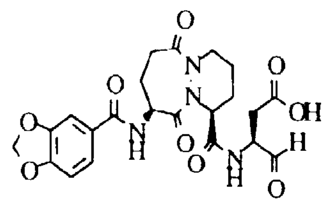
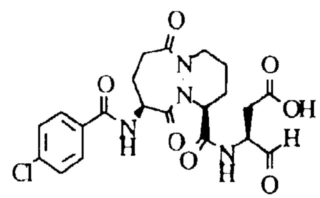
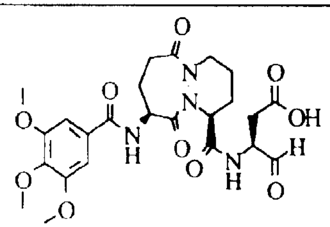
(5) Waters DeltaPak C18, 300A (5µ, 3.9 x 150 mm). Linear CH_3CN gradient (0% - 35%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

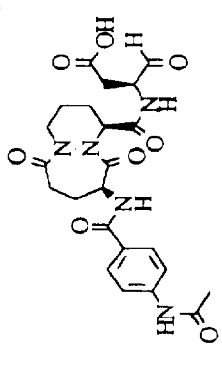
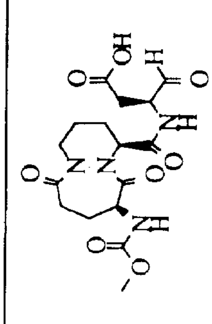
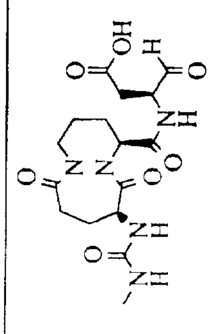
Table 7

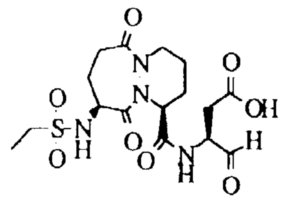
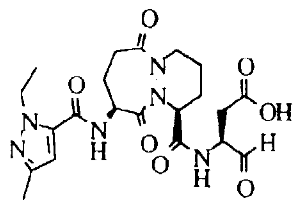
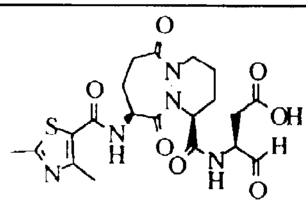
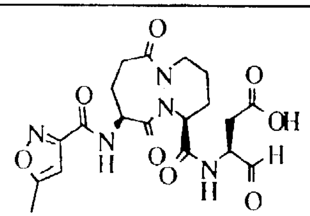
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
214e		C21H24N4O7	444.45	6.67 (2) 98%	445	2
404		C22H26N4O7	458.48	6.66 (2) 97%	459	2
405		C22H26N4O8	474.47	8.2 (1) 98%	475	2

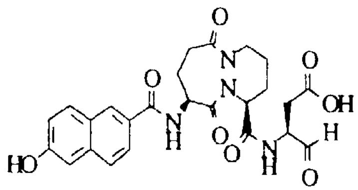
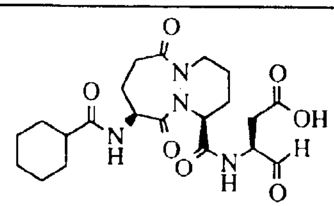
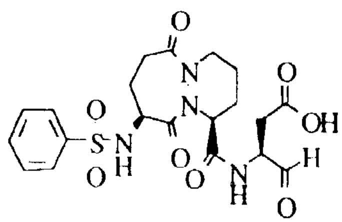
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
406		C21H23ClN4O7	478.89	6.33 (1) 98%	479	2
407		C25H26N4O7	494.51	9.90 (1) 98%	495	2
408		C25H26N4O7	494.51	9.0 (1) 98%	495	2
409		C27H28N4O7	520.55	11.14 (1) 98%	521	2

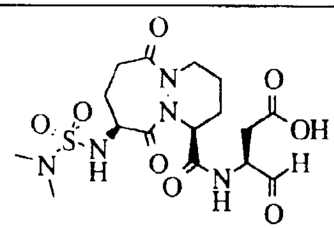
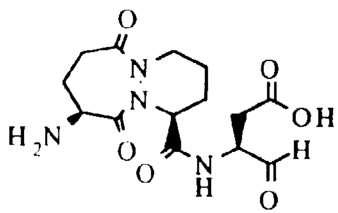
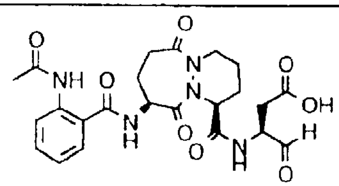
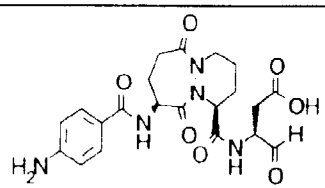
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
410		C19H22N4O7S	450.47	4.87 (1) 98%	451	1
411		C24H25N5O7	495.50	10.7 (1) 98%	496	1
412		C24H25N5O7	495.50	8.57 (1) 98%	496	1
413		C18H24N4O7	408.41	7.21 (2) 98%	409	1

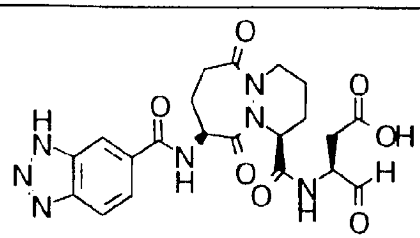
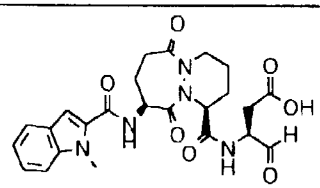
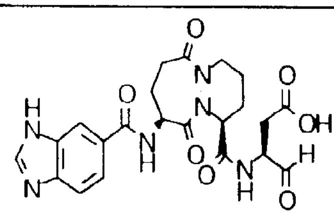
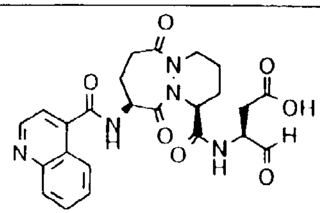
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
415		C22H24N4O9	488.46	7.58 (1) 98%	489	1
416		C21H23ClN4O7	478.89	9.66 (1) 98%	479	1
417		C24H30N4O10	534.53	8.12 (1) 535	535	1

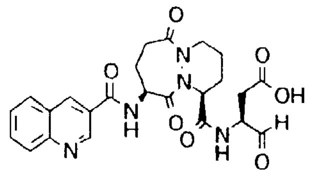
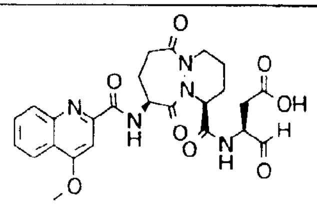
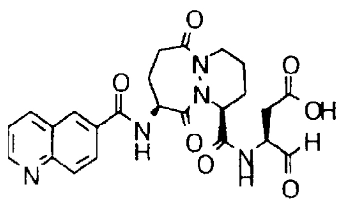
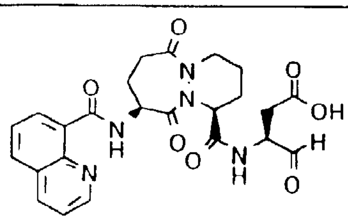
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
418		C23H27N5O8	501.50	5.93 (1) 98%	502	1A
419		C16H22N4O8	398.38	6.84 (2) 98%	399	2
420		C16H23N5O7	397.39	5.25 (2) 98%	398	4

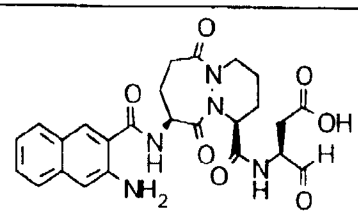
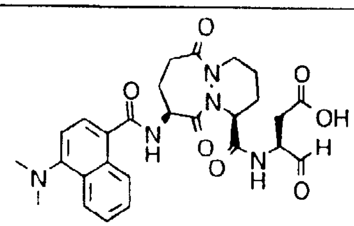
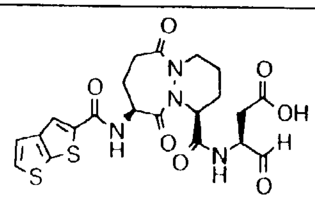
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
421		C16H24N4O8S	432.46	7.13 (2) 98%	433	3
422		C21H28N6O7	476.49	6.89 (1) 98%	477	1
423		C20H25N5O7S	479.52	5.62 (1) 98%	480	1
424		C19H23N5O8	449.42	6.28 (1) 450	450	1

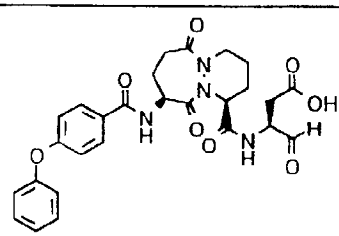
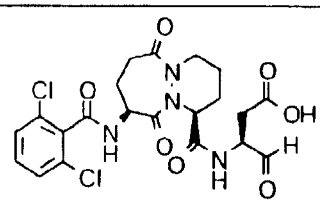
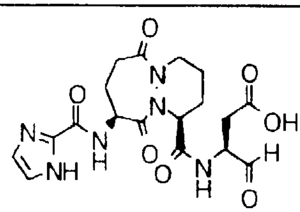
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
425		C25H26N4O8	510.51	8.25 (1) 98%	511	1
426		C21H30N4O7	450.50	8.0 (1) 98%	451	2
427		C20H24N4O8S	480.50	7.87 (1) 98%	481	3

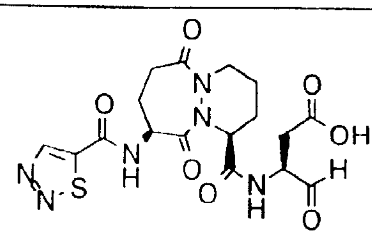
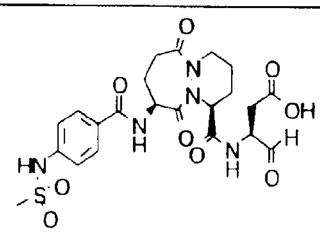
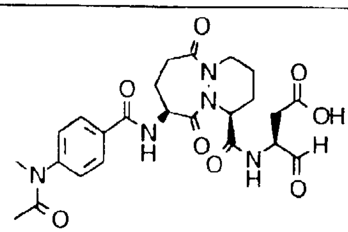
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
428		C16H25N5O8S	447.47	5.13 (1) 98%	448	3
429		C14H20N4O6	340.34	3.19 (3) 98%	341	
430		C23H27N5O8	501.50	5.53 (1) 98%	502	1A
431		C21H25N5O7	459.46	6.66 (2) 98%	460	1

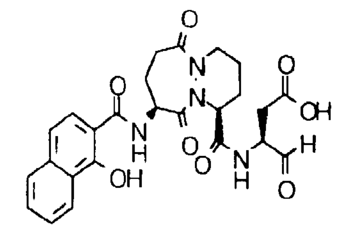
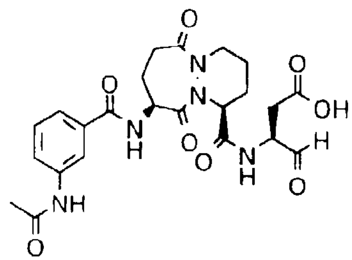
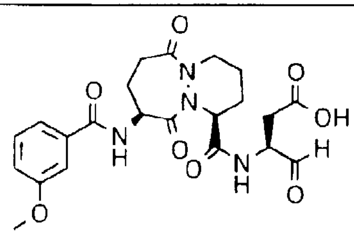
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
432		C21H23N7O7	485.46	5.59 (1) 98%	486	1
433		C24H27N5O7	497.51	11.07 (1) 97%	498	1
434		C22H24N6O7	484.47	4.43 (1) 98%	485	1
435		C24H25N5O7	495.50	5.10 (1) 98%	496	1

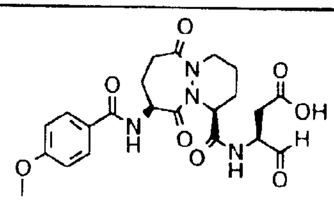
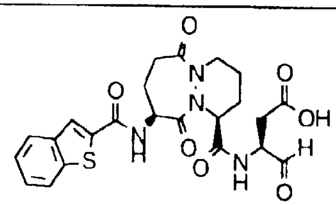
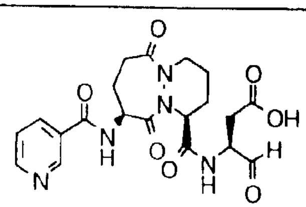
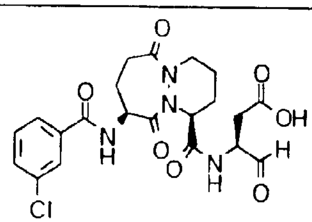
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
436		C24H25N5O7	495.50	8.20 (4) 98%	496	1
437		C25H27N5O8	525.52	12.78 (5) 98%	526	1
438		C24H25N5O7	495.50	4.85 (1) 98%	496	1
439		C24H25N5O7	495.50	8.70 (5) 98%	496	1

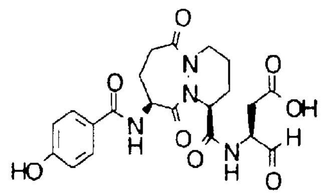
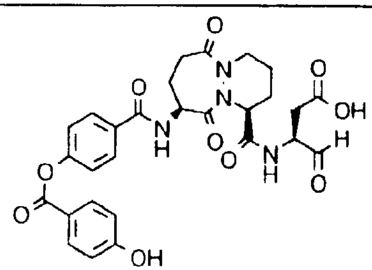
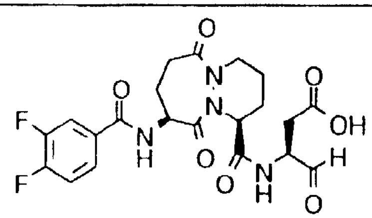
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
440		C25H27N5O7	509.52	9.96 (5) 98%	510	1
441		C27H31N5O7	537.58	6.15 (1) 98%	538	1
442		C21H22N4O7S2	506.56	10.10 (1) 98%	507	1

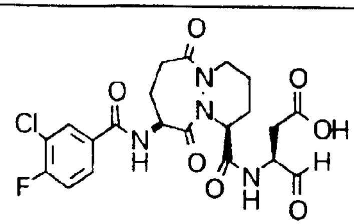
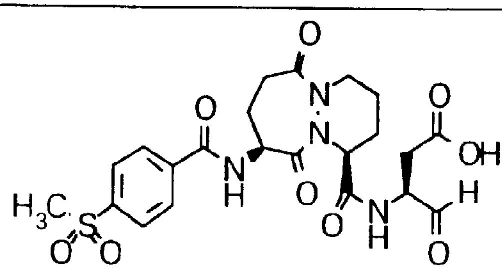
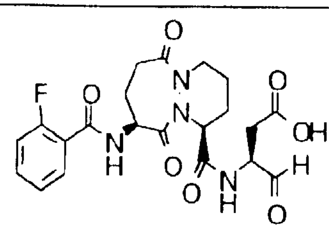
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
443		C27H28N4O8	536.55	13.12 (1) 98%	537	1
444		C21H22Cl2N4O7	513.34	9.96 (5) 98%	510	1
445		C18H22N6O7	434.41	5.72 (1) 98%	435	5

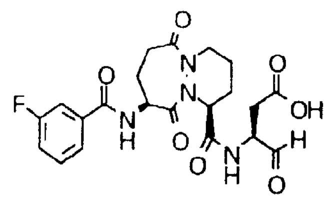
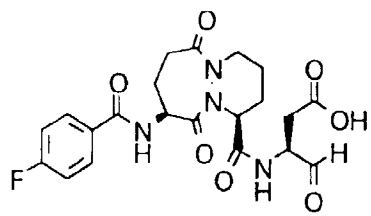
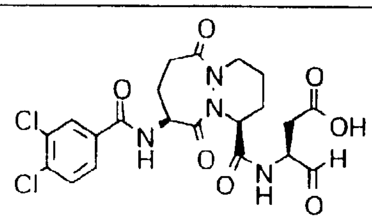
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
446		C17H20N6O7S	452.45	5.00 (1) 98%	453	1
447		C22H27N5O9S	537.55	6.32 (1) 98%	538	1B
448		C24H29N5O8	515.53	6.36 (1) 98%	516	1A

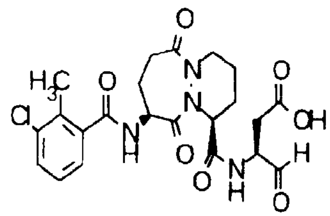
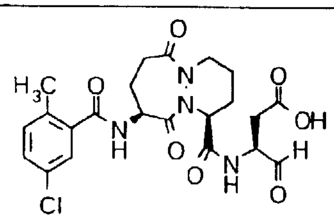
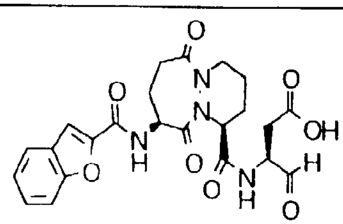
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
449		C25H26N4O8	510.51	13.86 (1) 98%	511	1
450		C23H27N5O8	501.50	6.10 (1) 98%	502	1A
451		C22H26N4O8	474.47	8.02 (1) 98%	475	2

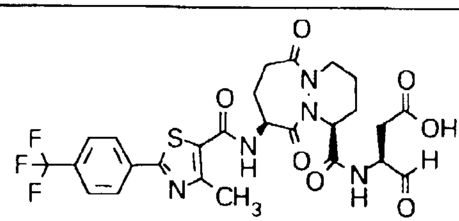
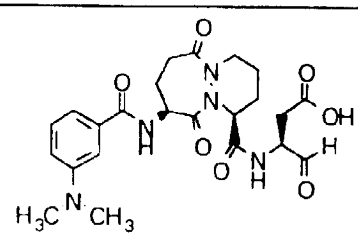
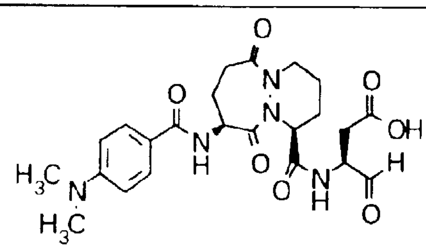
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
452		C22H26N4O8	474.47	7.77 (1) 98%	475	2
453		C23H24N4O7S	500.53	11.11 (1) 98%	501	2
454		C20H23N5O7	445.44	6.24 (2) 98%	446	2
455		C21H23ClN4O7	478.89	9.45 (1) 98%	479	2

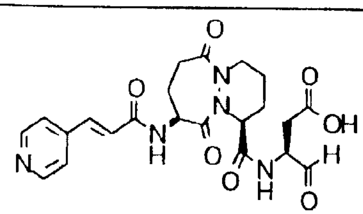
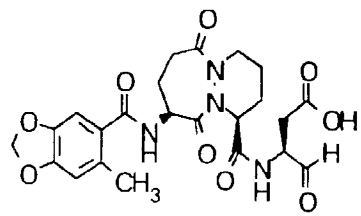
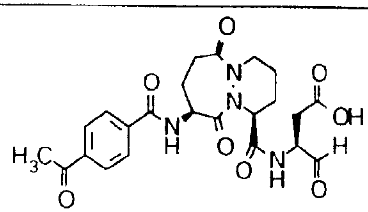
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
456		C21H24N4O8	460.45	5.58 (1) 98%	(M+Na) 483	1
457		C28H28N4O10	580.56	10.42 (1) 98%	(M+Na) 603	1
458		C21H22F2N4O7	480.43	8.65 (1) 98%	481.1	1

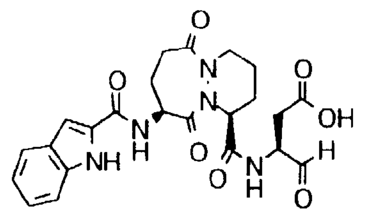
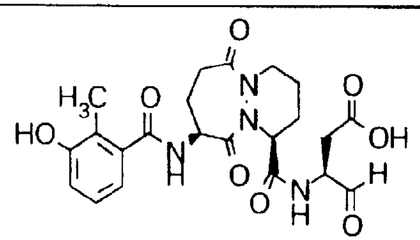
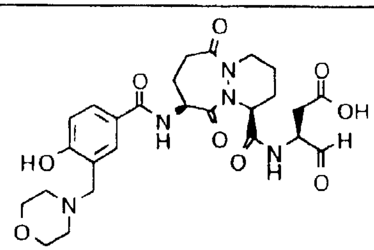
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
459		C21H22ClFN4O7	496.88	10.11 (1) 98%	498.3	1
460		C22H26N4O9S	522.54	6.16 (1) 98%	523.6	1
461		C21H23FN4O7	462.44	7.41 (1) 98%	463.3	1

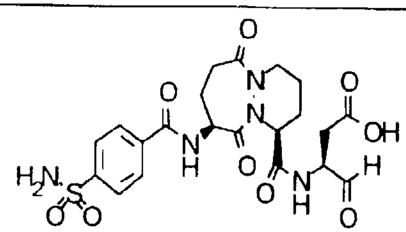
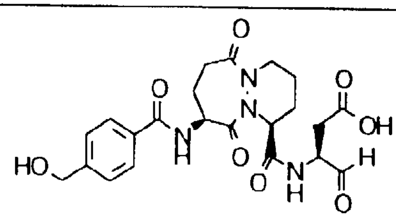
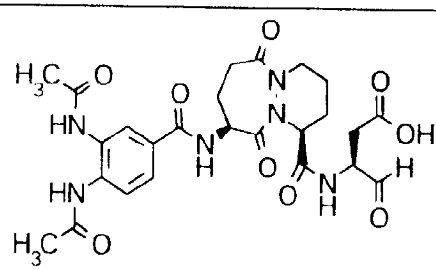
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
462		C21H23FN4O7	462.44	7.71 (1) 98%	463.3	1
463		C21H23FN4O7	462.44	7.64 (1) 98%	464	1
464		C21H22Cl2N4O7	513.34	11.59 (1) 98%	414.5	1

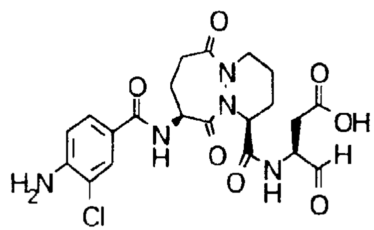
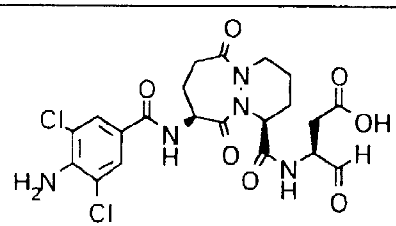
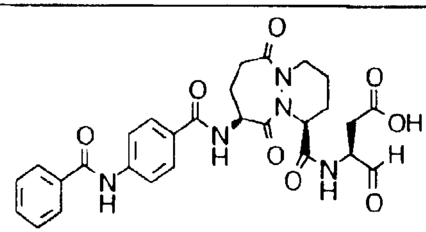
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
465		C22H25ClN4O7	492.92	9.65 (1) 98%	493.9	1
466		C22H25ClN4O7	492.92	9.63 (1) 98%	493.9	1
467		C23H24N4O8	484.47	9.73 (1) 98%	485.8	1

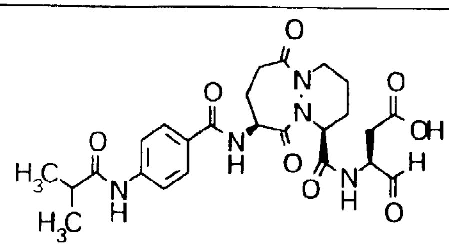
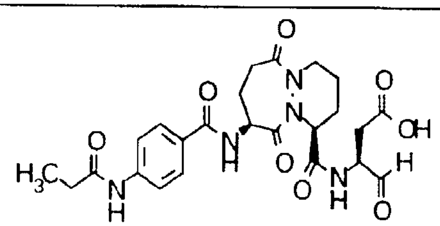
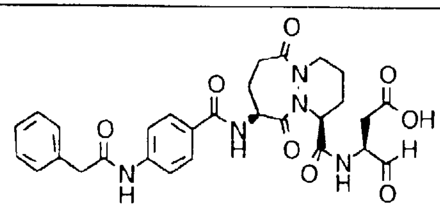
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
468		C26H26F3N5O7S	609.59	14.84 (1) 98%	609.7	1
470		C23H29N5O7	487.52	4.57 (1) 98%	489.5	1
471		C23H29N5O7	487.52	5.74 (1) 98%	488.2	1

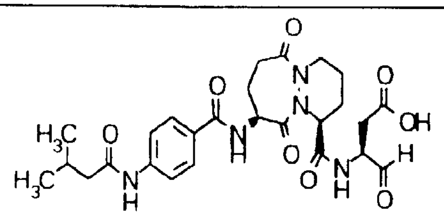
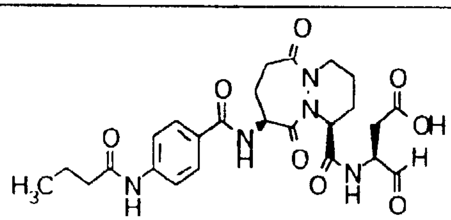
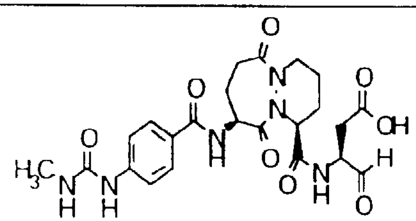
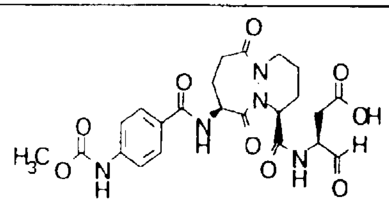
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
472		C22H25N5O7	471.47	4.00 (1) 98%	474	1
473		C23H26N4O9	502.49	7.65 (1) 98%	503.6	1
474		C23H26N4O8	486.49	7.16 (1) 98%	488.1	1

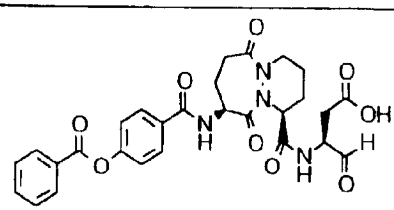
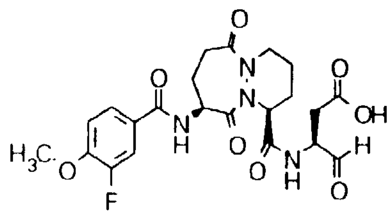
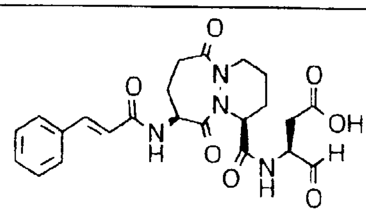
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
475		C23H25N5O7	483.49	9.77 (1) 97%	485.1	1
476		C22H26N4O8	474.47	5.25 (1) 98%	475.8	1
477		C26H33N5O9	559.58	4.76 (1) 95%	561.8	1

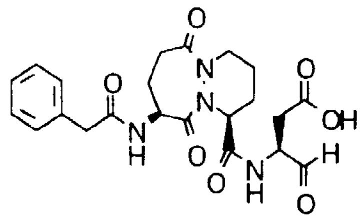
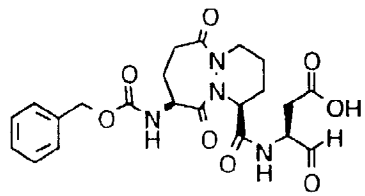
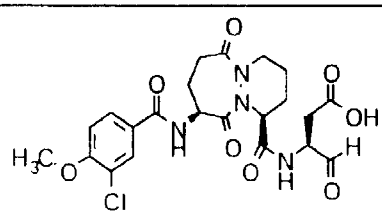
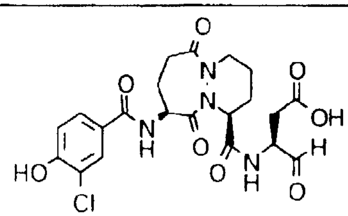
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
478		C21H25N5O9S	523.53	5.25 (1) 98%	524.3	1
479		C22H26N4O8	474.47	5.35 (1) 98%	475.8	1
480		C25H30N6O9	558.55	5.11 (1) 98%	559.3	1A

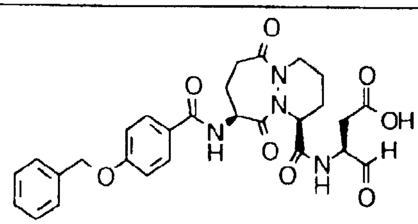
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
481		C21H24ClN5O7	493.9	7.10 (1) 98%	495.1	1
482		C21H23Cl2N5O7	528.4	9.05 (1) 98%	529.8	1
483		C28H29N5O8	563.57	10.01 (1) 98%	565.6	1,2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
484		C25H31N5O8	529.55	7.88 (1) 98%	531	1,2
485		C24H29N5O8	515.53	7.00 (1) 98%	517.6	1,2
486		C29H31N5O8	577.60	10.43 (1) 98%	579.4	1,2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
487		C26H33N5O8	543.58	9.30 (1) 98%	545.7	1,2
488		C25H31N5O8	529.55	8.13 (1) 98%	531.1	1,2
489		C23H28N6O8	516.52	5.89 (1) 98%	517.8	1,4
490		C23H27N5O9	517.50	7.27 (1) 98%	(M+Na) 540.8	1,2

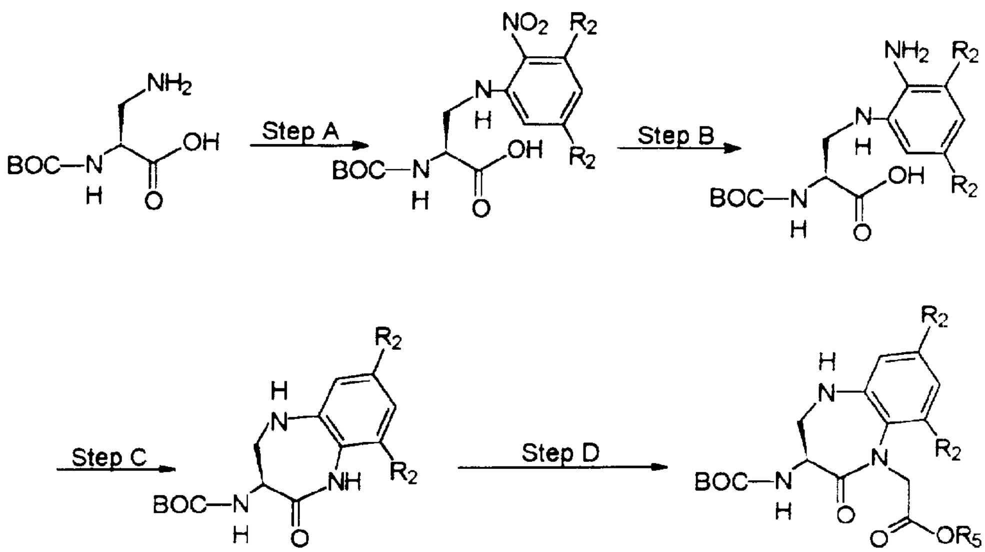
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
491		C28H28N4O9	564.56	12.9 (1) 98%	565.3	1
493		C22H25FN4O8	492.46	8.31 (1) 98%	493.9	1
494		C23H26N4O7	470.49	9.34 (1) 98%	471.2	2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
495		C22H26N4O7	458.48	7.24 (1) 98%	459.9	2
496		C22H26N4O8	474.47	9.47 (1) 98%	475.7	2
497		C22H25ClN4O8	508.92	9.58 (1) 98%	509.5	1
498		C21H23ClN4O8	494.89	7.18 (1) 98%	495.1	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
499		C28H30N4O8	550.57	13.27 (1) 98%	552	1

Example 12

Compounds **605a**-j, **605m**-q, **605s**, **605t**, and **605v** were synthesized as described below.



600

Compound no.	R_2	R_5
600a/103	H	CH_3
600b	H	CH_2Ph
600c	CH_3	CH_2Ph

(3*S*)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (**600a/103**).

Step A. **(2*S*)-2-*tert*-Butoxycarbonylamino-3-(2-nitrophenyl-amino)-propionic acid.** (2*S*)-2-*tert*-Butoxycarbonylamino-3-aminopropionic acid (10 g, 49 mmol), 2-fluoronitrobenzene (5.7 ml, 54 mmol), and $NaHCO_3$ (8.25 g, 98 mmol) was taken into 130 ml of DMF

and heated at 80 °C for 18 h. The reaction was evaporated *in vacuo* to give a viscous orange residue that was dissolved in 300 ml of H_2O and extracted with Et_2O (3 x 150 ml). The aq. solution was acidified to pH 5 with 10% $NaHSO_4$ and extracted with EtOAc (3 x 250 ml). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated to give 12.64 g (83%) of the title compound as an orange amorphous solid: ^1H NMR (CD_3OD) δ 8.15-8.10 (1H,d), 7.54-7.48 (1H,t), 7.13-7.08 (1H, d), 6.73-6.65 (1H, t), 4.45-4.35 (1H, m), 3.9-3.8 (1H, dd), 3.65-3.55 (1H, dd), 1.45 (9H, s).

__Step B__. **(2*S*)-2-*tert*-Butoxycarbonylamino-3-(2-aminophenyl-amino)-propionic acid.** A mixture of (2*S*)-2-tert-Butoxycarbonylamino-3-(2-nitrophenylamino)propionic acid (12.65 g, 40.5 mmol) and 0.5 g of 10% Pd/C in 100 ml of MeOH under hydrogen at 1 atmosphere was stirred for 4 h. The solution was filtered through Celite 545 and the filtrate evaporated *in vacuo* to afford the 11.95 g of the title compound in quantitative yield as a dark brown solid that was used without purification: ^1H NMR (CD_3OD) δ 6.75-6.70 (3H,m), 6.65-6.58 (1H, m), 4.35-4.3 1H, m), 3.6-3.38 (2H, m), 1.45 (9H, s).

__Step C__. **(3*S*)-2-Oxo-3-*tert*-Butoxycarbonylamino-1,3,4,5-tetrahydro-1H-1,5-benzodiazepine.** 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.54 g, 44.5 mmol) was added to a cooled (0 °C) solution of (2*S*)-2-*tert*-butoxycarbonylamino-3-(2-aminophenylamino)propionic acid (11.95 g, 40.5 mmol) in 100 ml of DMF and stirred for 18 h. The reaction was poured into 700 ml of EtOAc and washed four times with

100 ml of H_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to give a brown solid that was purified by flash chromatography eluting with 3:7 EtOAc/hexane to give 8 g (71%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 7.78 (1H, s), 7.02-6.95 (1H, m), 6.88-6.82 (1H, m), 6.82-6.78 (1H, m), 6.75-6.70 (1H, m), 5.8-5.7 (1H, d), 4.55-4.45 (1H, m), 3.95 (1H, s), 3.9-3.82 (1H, m), 3.48-3.40 (1H,m), 1.45 (9H,s).

<u>Step D</u>. (3*S*)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (600a/103). A 1.0 M solution of lithium bis(trimethylsilyl)amide (3.4 ml, 3.4 mmol) in THF was added dropwise to a -78 °C solution of (3*S*)-2-oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (0.94 g, 3.38 mmol) in 20 ml of anhydrous THF and stirred for 30 min. Methyl bromoacetate (o.44 ml, 4 mmol) was added dropwise to the reaction mixture then warmed to RT. The reaction was diluted with 100 ml of EtOAc and washed with 0.3N $KHSO_4$ (50 ml), H_2O (2 x 50 ml), and brine. The combined organics were dried over anhydrous Na_2SO_4, filtered, and evaporated to afforded a gum that was purified by flash chromatography eluting with 3:7 EtOAc/Hex. to give 0.98 g (83%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.15-7.07 (2H, m), 6.98-6.94 (1H, m), 6.88-6.84 (1H, d), 5.62-5.55 (1H, d), 4.71-4.65 (1H, d), 4.65-4.6 (1H, m), 4.33-4.27 (1H, d), 3.96-3.90 (1H, m), 3.78 (3H, s), 3.44-3.37 (1H, m), 1.4 (9H, s).

(3*S*)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (600b). Prepared by a similar method described for the preparation of **600a/103** (Step D), except benzyl bromoacetate was used instead of methyl bromoacetate to give **600b** in quantitative yield.

(3*S*)-2-Oxo3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (600c).

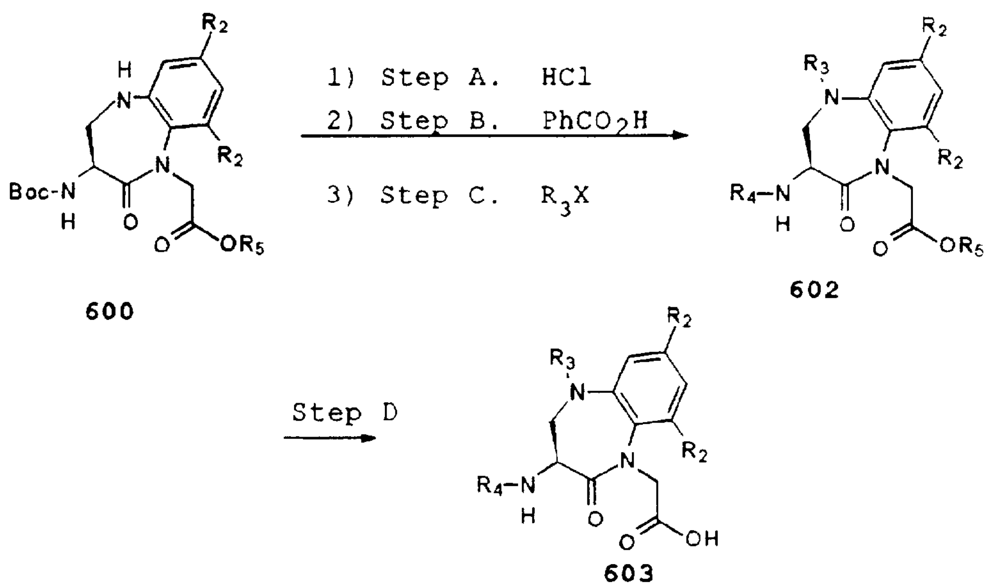
__Step A__. (2*S*)-2-*tert*-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenylamino)-propionic acid. Prepared by a method similar as described for **600a/103** (Step A), except 2-fluoro-4,6-dimethyl-nitrobenzene was used instead of 2-fluoronitrobenzene to give the desired compound in 93% yield.

__Step B__. **(2*S*)-2-*tert*-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid.** (2*S*)-2-*tert*-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenyl-amino)propionic acid was converted to the title compound in quantitive yield as described in the prepartation of **600a/103** (Step B).

__Step C__. **2-Oxo-(3*S*)-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine.** A 0 °C solution of (2*S*)-2-*tert*-butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid (763 mg, 2.36 mmol) and N-methylmorpholine (483 mg, 4.78 mmol) in 60 ml of anhydrous THF was treated dropwise with isobutylchloroformate (352 mg, 2.5 mmol). The reaction was stirred for 2 h at 0 °C, at RT for 1h and poured over EtOAc. The mixture was washed with aq. 5% $NaHSO_4$,

sat. aq. $NaHCO_3$, and sat. aq. NaCl, dried over $NaSO_4$, and concentrated *in vacuo*. Chromatography (flash, SiO_2, 10% to 25% to 50 % EtOAc/CH_2Cl_2) gave 490 mg (68%) of the desired product.

Step D. (3*S*)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600c). (2*S*)-2-*tert*-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid was converted to **600c**, 75% by a similar method for the preparation of **600b**.



(3*S*)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzo diazepine-1-acetic acid methyl ester (602a).

Step A. Anhydrous HCl was bubbled into a solution of (3*S*)-2-oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (**600a/103**, 4.0 g, 11.4 mmol) in 20 ml of CH_2Cl_2 for 20 min then stirred for 1 h at RT. The reaction

was evaporated to give (3*S*)-2-oxo-3-amino-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester hydrochloride as a white solid.

Step B. The white solid was dissolved in 70 ml of DMF and benzoic acid (1.5 g, 12.3 mmol) was added. The reaction was cooled in a ice/H_2O bath and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.4 g, 12.5 mmol), 1-hydroxybenzotriazole (1.7 g, 12.6 mmol) and diisopropylethylamine (3.0g, 23.2 mmol). The reaction was stirred for 18 h at RT under nitrogen atmosphere and poured onto H_2O. The aq. mixture was extracted with EtOAc (2x). The combined organic layers were washed with aq. 0.5 N $NaHSO_4$, H_2O, sat. aq. $NaHCO_3$, H_2O and sat. aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography (flash, SiO_2, 10% to 30% EtOAc/CH_2Cl_2) gave 3.4 g (85%) of (3*S*)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester as a white solid.

Step C. **Method A**. **(3*S*)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (602a)**. A solution of (3*S*)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (200 mg, 0.57 mmol) in CH_2Cl_2(10 ml) was treated with triethylamine (119 mg, 1.13 mmol) and 3-phenylpropionyl chloride (114 mg, 0.68 mmol). The reaction was stirred at RT for 30 min and diluted with CH_2Cl_2. The solution was washed with aq. 10% HCl, sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over Na_2SO_4 and

concentrated *in vacuo* to give 240 mg (87%) of **602a** as a white foam.

Step C. Method B. (3*S*)-2-Oxo-3-benzoylamino-5-acetoacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (602g). A 0 °C solution of (3*S*)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (**600b**) (465 mg, 1.10 mmol) in CH_2Cl_2 (5 ml) was treated with acetoacetic acid in 1 ml of CH_2Cl_2 followed by slow addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (431 mg, 2.2 mmol) in 2 ml of CH_2Cl_2 under N_2 atmosphere. After 15 min the reaction was poured onto EtOAc, washed with aq. 5 % $NaHSO_4$, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (flash, SiO_2, 0% to 10% to 25% $MeOH/CH_2Cl_2$) gave 580 mg of (3*S*)-2-oxo-3-(benzoylamino)-5-acetoacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester as a white solid.

Step C. Method C. (3*S*)-2-Oxo-3-benzoylamino-5-methoxycarbonyl-2,3,4,5-tetrahydro-1*H*-1,5-benzo diazepine-1-acetic acid benzyl ester (602j). A vigorously-stirred, 0 °C solution of (3*S*)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (**600b**) (461 mg, 1.07 mmol) in THF (5 ml) and sat. aq. $NaHCO_3$ (2.5 ml) was treated with a THF solution (0.35 ml) of methyl chloroformate (151 mg, 1.6 mmol) and the reaction was stirred for 45 min at RT. The reaction was poured onto CH_2Cl_2 and washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography

(flash, SiO_2, 0% to 10% $MeOH/CH_2Cl_2$) gave 525 mg of **602j** as a white solid.

<u>Step C</u>. <u>Method D</u>. **(3*S*)-2-Oxo-3-benzoylamino-5-benzylaminocarbonyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (602p).** A solution of **600a/103** (400 mg, 1.1mmol) and benzylisocyanate (166 mg, 1.2mmol) in 10 ml of CH_2Cl_2 and 10 ml of DMF and heated at 80 °C for 3 days. The reaction was cooled to RT poured onto H_2O and extracted with EtOAc (2x). The combined organic layers were washed with H_2O (4x) and sat. aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography (flash, SiO_2, 50% to 80% EtOAc/hexane) gave 440 mg (80%) of **602p** as a white solid.

<u>Step C</u>. <u>Method E</u>. **(3*S*) 2-Oxo-3-benzylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (602v).** A solution of (3S) 2-oxo-3-amino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester hydrochloride (560 mg, 1.34 mmol), benzaldehyde (146 mg, 1.34 mmol) and sodium acetate (220 mg, 2.68 mmol) in methanol (20 ml) was treated with 4Å sieves (2 g) and $NaCNBH_3$ (168 mg, 2.68 mmol). The reaction was stirred for 2.5 h, acidified with 10% aq. HCl to pH 2 and washed with Et_2O (2x75 ml). The organic layers were concentrated *in vacuo* to give an oil. Chromatography (flash, SiO_2, 0 to 35% $EtOAc/CH_2Cl_2$) gave 250 mg (40%) of **602v** as a clear oil.

<u>Step D</u>. <u>Method A</u>. **(3*S*)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1*H*-1,5-**

benzodiazepine-1-acetic acid (603a). (3*S*)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzo diazepine-1-acetic acid methyl ester (**602a**; 1.25 g, 2.57 mmol) was dissolved in 11 ml of THF, MeOH and H_2O (5:5:1) and treated with LiOH•H_2O (42 mg, 0.62 mmol) stirred at RT for 64 h. The reaction was concentrated *in vacuo*, diluted with H_2O and acidified with aq. 1N HCl to give 230 mg of **603a** as a white solid.

__Step D__. __Method B__. **(3*S*) 2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid (603d).** A mixture of (3*S*)-2-oxo-3-(benzoylamino)-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (**602d**; 510 mg, 1.08 mmol) and 5% Pd/C (250 mg) in MeOH (10 ml) stirred under H_2 (1 atm) for 0.5h. The reaction was filtered and concentrated *in vacuo* 410 mg of **603d** as a white solid.

The compounds of Table 8 were prepared as described in Table 9, using the methods of Example 12.

__Table 8__

Compound no.	R_2	R_3	R_4	R_5
602b	H	$PhCH_2C(O)$	PhC(O)	CH_2Ph
602c	H	PhC(O)	PhC(O)	CH_2Ph
602d	H	$CH_3C(O)$	PhC(O)	CH_2Ph
602e	H	$CH_3OCH_2C(O)$	PhC(O)	CH_2Ph
602f	H	$(CH_3)_2CHCH_2C(O)$	PhC(O)	CH_2Ph
602g	H	$CH_3C(O)CH_2C(O)$	PhC(O)	CH_2Ph

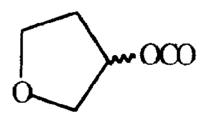
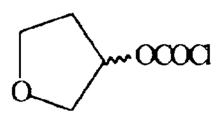
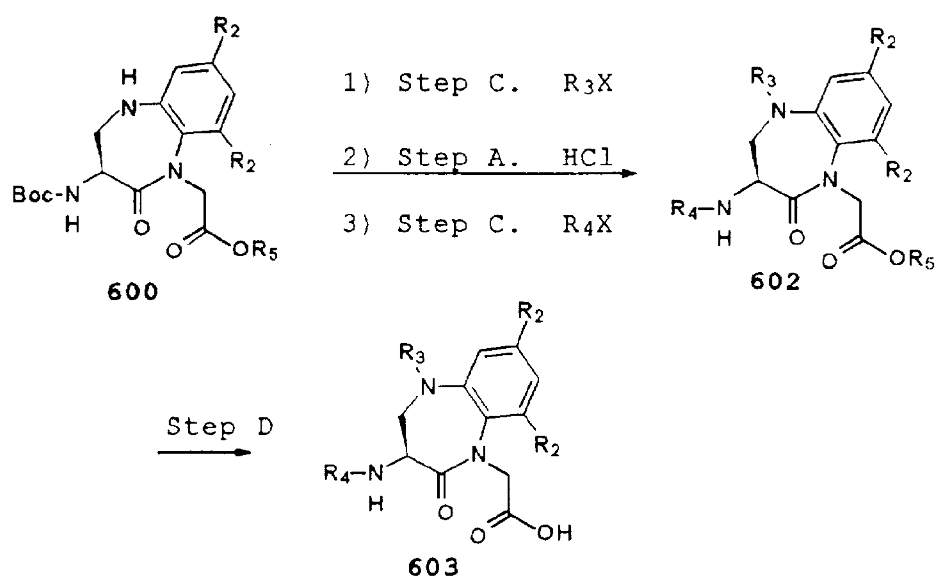
Compound no.	R_2	R_3	R_4	R_5
602h	H	$CH_3OC(O)C(O)$	PhC(O)	CH_2Ph
602i	H	$CH_3C(O)C(O)$	PhC(O)	CH_2Ph
602j	H	$CH_3OC(O)$	PhC(O)	CH_2Ph
602k	H	$CH_3C(O)$	Boc	CH_2Ph
602l	CH3	$CH_3C(O)$	Boc	CH_2Ph
602m	H	CH3S(O2)	PhC(O)	CH_3
602p	H	$PhCH_2NHC(O)$	PhC(O)	CH_3
602q	H		PhC(O)	CH_2Ph
602r	H	$PhCH_2CH_2C(O)$	$PhCH_2CH_2C(O)$	CH_2Ph
602s	H	4-pyridyl$CH_2C(O)$	PhC(O)	CH_2Ph

Table 9

No.	Starting material	R_3X	Step C method/ (% yield)	Step D method/ (% yield)
603b	**600b**	$PhCH_2C(O)Cl$	A (98)	B (89)
603c	**600b**	PhC(O)Cl	A (quant.)	B (quant.)
603d	**600b**	$CH_3C(O)Cl$	A (quant.)	B (quant.)
603e	**600b**	$CH_3OCH_2C(O)Cl$	A (59)	B (quant.)
603f	**600b**	$(CH_3)_2CHCH_2C(O)Cl$	A (88)	B (95)
603g	**600b**	$CH_3C(O)CH_2CO_2H$	B (quant.)	B (quant.)
603h	**600b**	$CH_3OC(O)C(O)Cl$	A (96)	B (quant.)
603i	**600b**	$CH_3C(O)CO_2H$	B (87)	B (94)
603j	**600b**	$CH_3OC(O)Cl$	C (quant.)	B (quant.)

No.	Starting material	R_3X	Step C method/ (% yield)	Step D method/ (% yield)
603k	**600b**	$CH_3C(O)Cl$	A, Step C only (quant.)	not run
603l	**600c**	$CH_3C(O)Cl$	A, Step C only (quant.)	not run
603m	**600a/103**	CH_3SO_3Cl, NEt_3 instead of pyridine and THF instead of CH_2Cl_2	A (76)	A (92)
603p	**600a/103**	$PhCH_2C=N=O$	D (80)	A (86)
603q	**600b**		C (83)	B (71)
603r	**600a/103**	$PhCH_2CH_2C(O)Cl$	A	
603s	**600b**	4-pyridylCH_2CO_2H	B (90)	B (98)



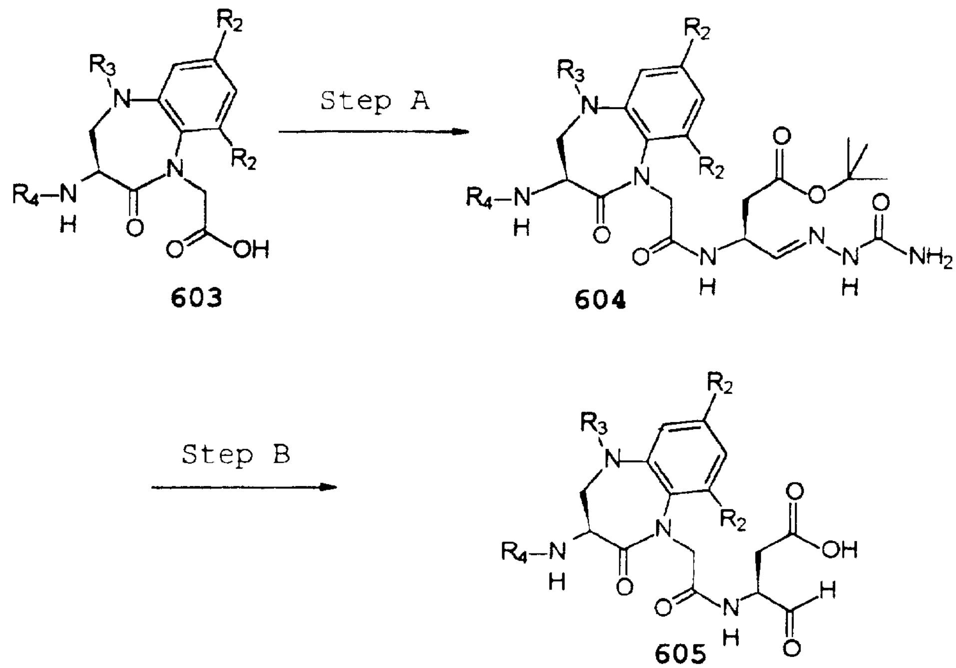
The compounds of Table 10 were prepared as described in Table 11 using the methods of Example 12.

Table 10

Compound no.	R_2	R_3	R_4	R_5
602n	H	$CH_3C(O)$	Naphthylene-2-C(O)	CH_2Ph
602o	CH_3	$CH_3C(O)$	PhC(O)	CH_2Ph
602t	H	3-$CH_3PhCH_2C(O)$	PhC(O)	CH_2Ph
602u	H	$CH_3C(O)$	Fmoc	CH_2Ph
602v	H	$PhCH_2CH_2CO$	$PhCH_2$	CH_3

Table 11

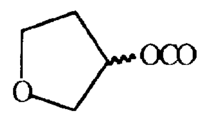
No.	Starting material	1) Step C. R_3X method (% yield)	3) Step C R_4X method (% yield)	Step D method (% yield)
603n	602k	$CH_3C(O)Cl$ A (quant.)	naphthylene-2-C(O)Cl A (70)	B(quant.)
603o	602l	$CH_3C(O)Cl$ A (quant.)	PhC(O)Cl A (73)	B(quant.)
603t	602k	3-$CH_3PhCH_2C(O)Cl$ A (quant.)	PhC(O)Cl A (93)	B (95)
603u	602k	$CH_3C(O)Cl$ A (quant.)	Fmoc-Cl C (82)	C (98)
603v	600a/103	$PhCH_2CH_2C(O)Cl$ A	PhCHO E(40)	A (95)



The compounds of Table 12 were prepared by the methods described below.

Table 12

compound no.	R_2	R_3	R_4
605a	H	$PhCH_2CH_2C(O)$	PhC(O)
605b	H	$PhCH_2C(O)$	PhC(O)
605c	H	PhC(O)	PhC(O)
605d	H	$CH_3C(O)$	PhC(O)
605e	H	$CH_3OCH_2C(O)$	PhC(O)
605f	H	$(CH_3)_2CHCH_2C(O)$	PhC(O)
605g	H	$CH_3C(O)CH_2C(O)$	PhC(O)
605h	H	$CH_3OC(O)C(O)$	PhC(O)
605i	H	$CH_3C(O)C(O)$	PhC(O)
605j	H	$CH_3OC(O)$	PhC(O)

compound no.	R_2	R_3	R_4
605m	H	CH3SO3	PhC(O)
605n	H	$CH_3C(O)$	Naphthyl-2-C(O)
605o	CH_3	$CH_3C(O)$	PhC(O)
605p	H	$PhCH_2NHC(O)$	PhC(O)
605q	H		PhC(O)
605s	H	4-pyridyl$CH_2C(O)$	PhC(O)
605t	H	3-$CH_3PhCH_2C(O)$	PhC(O)
605v	H	$PhCH_2CH_2C(O)$	$PhCH_2$

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605a).

<u>**Step A**</u>. (3*S*)-3-(1-Fluorenylmethyloxycarbonylamino)-4-oxobutyric acid tert-butyl ester semicarbazone (210 mg, 0.45 mol, Prepared in a similar manner to the benzyloxycarbonyl analog in Graybill et al., <u>Int. J. Protein Res.</u> , 44, pp. 173-82 (1994).) was dissolved in 10 ml of DMF and 2 ml of diethylamine and stirred for 2 h. The reaction was concentrated *in vacuo* to give (3*S*)-3-amino-4-oxobutyric acid tert-butyl ester semicarbazone. The 0 °C solution of the above residue and **603a** (200 mg, 0.42mmol) in 5 ml of DMF and 5 ml of CH_2Cl_2 was treated with 1-hydroxybenzotriazole (57 mg, 0.42mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (98 mg, 0.51 mmol). The reaction was stirred at RT for 18 h, poured onto

EtOAc (75 ml) and washed with aq. 0.3 N $KHSO_4$, sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over $NaSO_4$ and concentrated *in vacuo*. Chromatography (flash, SiO_2, 0% to 4% MeOH/0.1% NH_4OH/CH_2Cl_2) to give 240 mg (83%) of **604a**.

<u>**Step B**</u>. **604a** was stirred with 10 ml of 33% TFA/H_2O for 4 h and concentrated *in vacuo*. The residue was dissolved in 7 ml of MeOH/acetic acid/37% aq. formaldehyde (5:1:1) and stirred for 18 h. Chromatography (Reverse Phase C18, 4.4mm ID x 25 cm, 15% to 70% CH_3CN/0.1% TFA/H_2O) gave 32 mg (16%) of **605a** as a white solid: ^1H NMR (CD_3OD, existing as diastereomers of the hemiacetal) δ 7.85-7.78 (2H, d), 7.5-7.32 (6H, m), 7.32-7.28 (1H, m), 7.18-6.98 (5H, m), 4.92-4.85 (2H, m), 4.5-4.32 (2H, m), 4.31-4.20 (2H, m), 3.7-3.6 (1H, m), 2.90-2.75 (2H, m), 2.65-2.5 (1H, m), 2.48-2.25 (3H, m).

The following compounds were prepared by a similar method:

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-phenylacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605b). 148 mg (33%) as a white solid: ^1H NMR(CD_3OD) δ 7.9-6.9 (m, 16H), 4.9 (s, 2H), 4.5 (m, 1H), 4.4 (m, 2H), 3.75 (s, 1H), 3.6 (dd, 1H), 3.45 (dd, 1H), 2.7 (m, 1H), 2.5 (m, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-benzoyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605c). 319 mg (56%) as a white solid: ^1H NMR(CD_3OD) δ 7.9-6.9 (m, 16H), 5.1 (m, 1H), 4.9 (dd,

1H), 4.7 (m, 1H), 4.6 (dd, 1H), 4.4 (m, 2H), 4.05 (m, 1H), 2.7 (m, 1H), 2.5 (m, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605d). 190 mg (38%) as a white solid: ^{1}H NMR(CD_3OD) δ 1.9(d, H), 2.4(m, 1H), 2.65(m, 1H), 3.7(m, 1H), 4.25(m, 1H), 4.45(m, 2H), 4.8-5.05(m, 3H), 7.3-7.7(m, 7H), 7.9(d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605e). 250 mg (78%) ^{1}H NMR (CD_3OD) δ 1.87 (bs), 1.95 (s, 2H), 2.1 (bs), 2.4 (m, 2H), 2.65 (m, 2H), 3.59 (bs), 3.75 (bs), 3.87 (bs), 4.19 (m), 4.37 (m), 4.50-4.78 (bm), 4.92 (m), 5.27 (bs), 7.41-7.58 (m, 7H), and 7.87 ppm (d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(3-methylbutyryl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605f). 210.5 mg (46%) as a white solid: ^{1}H NMR(CD_3OD) δ 7.9-7.4 (m, 9H), 5.1 (m, 1H), 4.9 (m, 1H), 4.6 (dd, 1H), 4.4 (m, 2H), 4.1 (d, 1H), 3.8 (m, 1H), 3.5 (q, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.0 (m, 3H), 1.2 (t, 1H), 0.9 (d, 3H), 0.8 (d, 3H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-acetoacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605g). 81 mg (19%) as a white solid: ^{1}H NMR(CD_3OD) δ 7.9-7.3 (m, 11H), 4.9-4.8 (m, 2H), 4.6-4.4 (m, 3H), 4.3 (m, 1H), 3.75 (q,

1H), 3.55 (d, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.05 (s, 3H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-methyloxalyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605h). 227 mg (54%) of a white solid: ^{1}H NMR(CD_3OD) δ 2.5(m, 1H), 2.7(m, 1H), 3.55(s, 3H), 3.8-4.0(m, 2H), 4.4(m, 1H), 4.6-4.8(m, 2H), 4.95(d, 1H), 5.1(m, 1H), 7.3-7.7(m, 7H), 7.9(d, 2H), 8.6(d, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-acetylcarbonyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605i). 150 mg (37%) as a white solid: ^{1}H NMR(CD_3OD) δ 7.9-7.3 (m, 12H), 5.1 (m, 1H), 4.65 (t, 1H), 4.55 (dd, 1H), 4.35 (m, 1H), 4.1 (d, 1H), 3.9 (q, 1H), 3.45 (q, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.25 (s, 3H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-methoxycarbonyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605j). 234 mg (44%) as a white solid: ^{1}H NMR(CD_3OD) δ 7.9-7.4 (m, 12H), 5.0 (m, 1H), 4.8-4.5 (m, 3H), 4.4 (m, 1H), 4.3 (t, 1H), 3.9-3.75 (m, 2H), 3.6 (s, 3H), 2.7 (m, 1H), 2.5 (m, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-methanesulfonyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605m). 64.5 mg (34%) as a white solid: ^{1}H NMR (DMSO-d_6, exisitng as diastereomers of the hemiacetal & open form of the aldehyde) δ 9.48 (0.2H, s), 8.85-8.72 (1H, m), 8.65-

8.60 (0.8 H, d), 8.30-8.26 (0.2 H, d), 7.95-7.88 (2H,d), 7.6-7.45 (6H, m), 7.44-7.38 (1H, m), 5.78-5.75 (0.2H, d), 5.48 (0.6H, s), 4.85-4.70 (2H, m), 4.62-4.54 (1H, d), 4.50-4.40 (2H, m), 4.25-4.14 (1H, m), 3.9-3.85 (1H, m), 3.16 (3H, s), 3.05-2.3 (2, m).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(naphthlene-2-carbonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605n). 103 mg (17%) as a white solid: ^{1}H NMR (CD_3OD) δ 1.9(s, 3H), 2.5(m, 1H), 2.65(m, 1H), 3.75(m, 1H), 4.3(m,1H), 4.5-4.7(m, 3H), 4.85-5.1(m, 2H), 7.3-7.65(m, 6H), 7.85-8.05(m, 4H), 8.45(s, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605o). 42 mg (12%) as a white solid: ^{1}H NMR (CD_3OD, existing as diastereomers of the hemiacetal) δ 7.85-7.74 (2H, m), 7.5-7.44 (1H, m), 7.43-7.35 (4H, m), 5.6-5.05 (2H, m), 4.82-4.42 (2H, m), 4.40-3.95 (2H, m), 3.6-3.5 (1H, m), 2.7-2.38 (2H, m), 2.32 (3H, s), 2.27 (3H, s), 1.92 (3H,s).

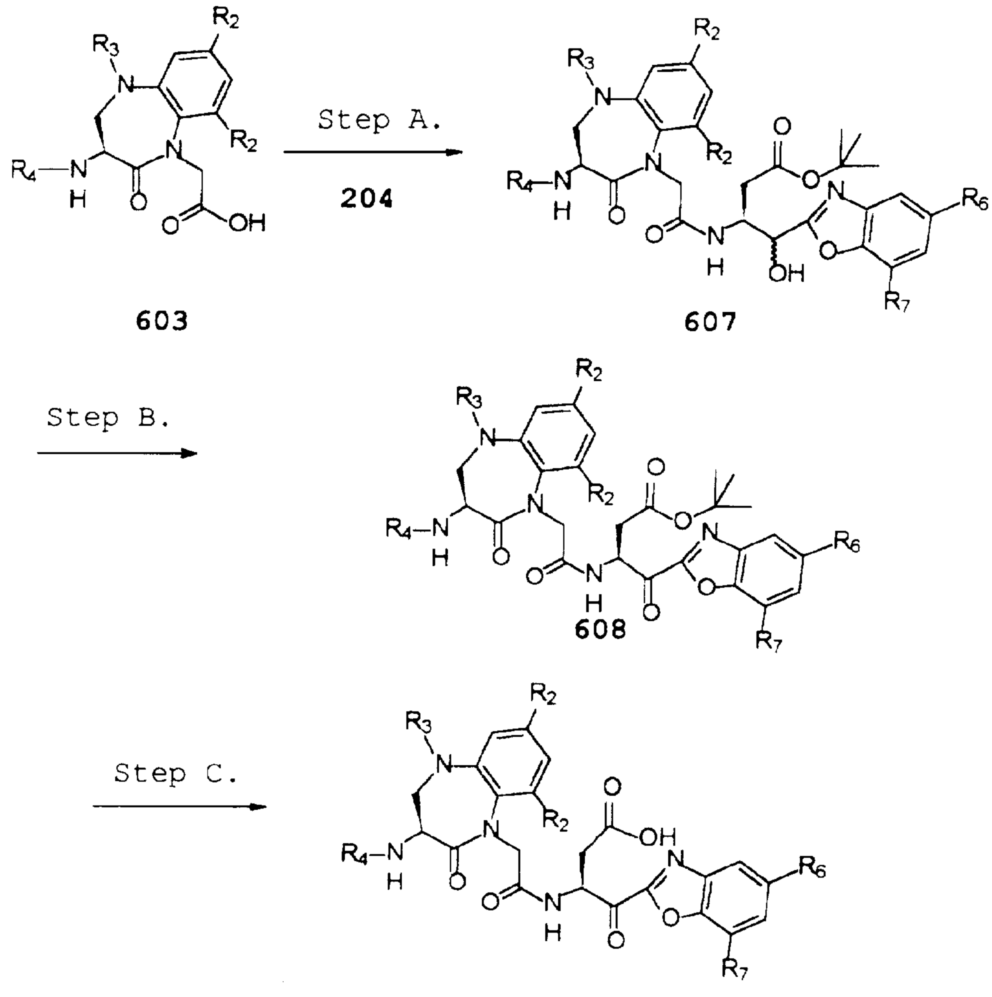
(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-benzylaminocarbonyl-2,3,4,5-tetrahydro-1*H*-1,5-benzo diazepin-1-acetylamino]4-oxo-butyric acid (605p). 165 mg (37%) as a white solid: ^{1}H NMR (CD_3OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.8(m, 1H), 4.15-4.5(m, 4H), 4.5-4.75(m, 2H), 4.8-5.0(m, 2H), 7.1-7.7(m, 12H), 7.9(d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-[(3*R,S*) 3-tetrahydrofuranylmethyoxycarbonyl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605q). 210 mg (66%) ^{1}H NMR (CD_3OD) δ 1.95 (s, 2H), 2.4 (m, 2H), 2.65 (m, 2H), 3.29 (s, 3H), 3.78 (m), 3.87 (bs), 4.0 (d, 1H), 4.32 (m), 4.50-4.15 (m), 4.95 (m), 5.27 (bs), 7.45-7.65 (m, 7H), and 7.89 ppm (d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(4-pyridylacetyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605s). 128 mg (19%) as a white solid: ^{1}H NMR(CD_3OD) δ 8.5-7.4 (m, 13H), 5.0 (m, 1H), 4.7 (m, 1H), 4.5 (m, 2H), 4.45-4.4 (m, 3H), 3.8-3.7 (m, 2H), 2.7 (m, 1H), 2.5 (m, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(3-methylphenylacetyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605t). 132 mg (24%) as a white solid: ^{1}H NMR(CD_3OD) δ 7.8-6.7 (m, 13H), 4.9 (t, 1H), 4.75 (dd, 1H), 4.2 (dd, 1H), 4.1 (m, 2H), 3.8 (dd, 1H), 3.6 (q, 1H), 3.45 (dd, 1H), 3.3 (dd, 1H), 2.6 (m, 1H), 2.3 (m, 1H), 2.15 (s, 3H).

(3*S*) 3-[(3S) 2-Oxo-3-benzylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid trifluoroacetic acid salt (605v). 88 mg (28%) as a white solid: ^{1}H NMR (CD_3OD) δ 7.63-7.51 (2H, m), 7.5-7.35 (7H, m), 7.25-7.10 (3H,m), 7.1-7.02 (2H, m), 5.04-4.96 (1H, m), 4.75-4.57 (2H, m), 4.38-4.[illegible] (2H,m), 4.24-4.12 (2H, m), 4.10-4.02 (1H, d), 4.88-4.[illegible] (1H, m), 2.90-2.80 (2H, m), 2.78-2.63 (1H,m), 2.55-2.35 (2H, m), 2.34-2.22 (1H, m).



603 607 608 609

The compounds of Table 13 are described below.

Table 13

#	R_2	R_3	R_4	R_6	R_7
609a	H	$PhCH_2CH_2C(O)$	$PhCH_2CH_2C(O)$	Cl	Cl
609b	H	$CH_3C(O)$	PhC(O)	Cl	Cl

(3*S*)-3-[(3*S*)-2-Oxo-3-(3-phenylpropionylamino)-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609a).

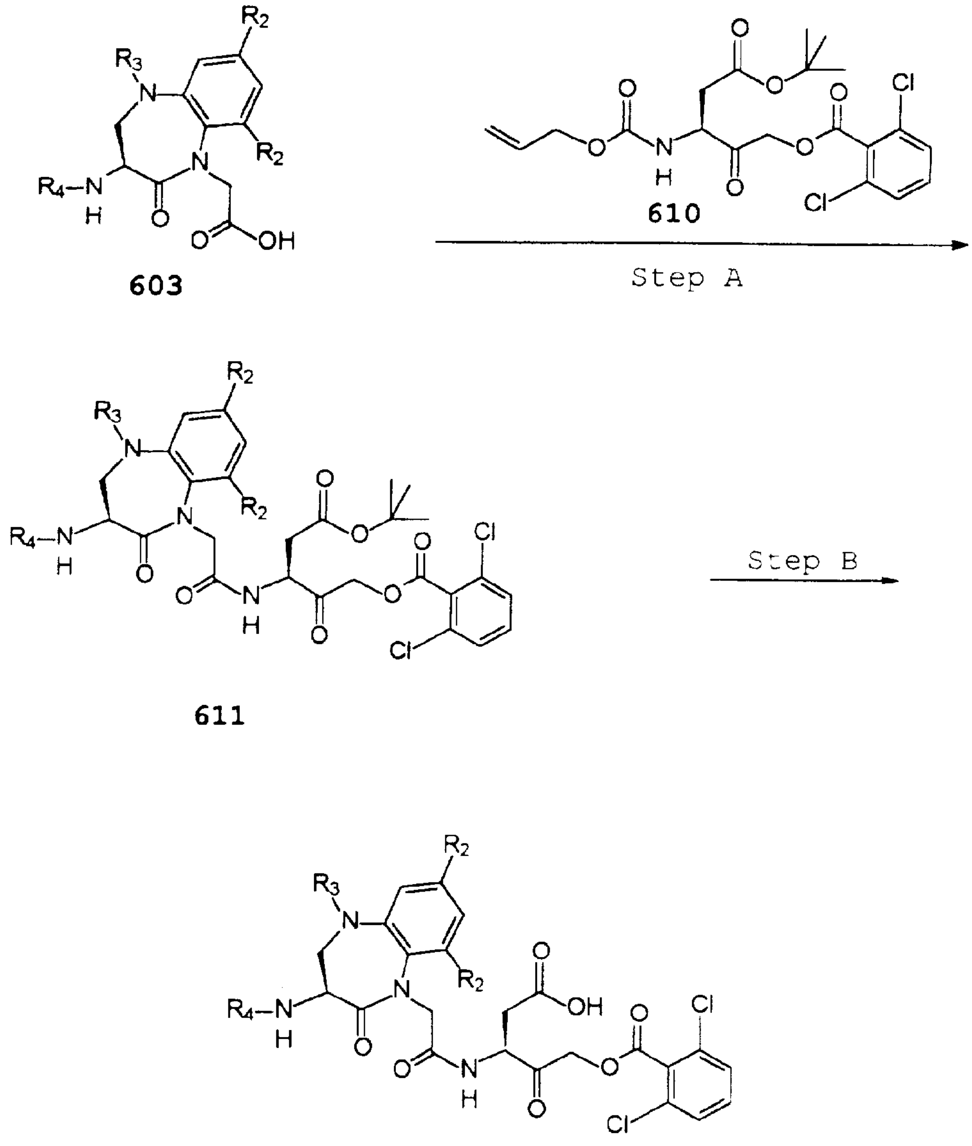
Step A. A solution of **204** (223 mg, 0.5 mmol) and **603r** (300mg; 0.36 mmol) in 4 ml of DMF and 4 ml of CH_2Cl_2 was treated with $(Ph_3P)_2PdCl_2$ (10 mg), 1-hydroxybenzotriazle (135 mg, 1.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (115 mg, 0.6 mmol). Tri-n-butyl tin hydride (219 mg, 0.75 mmol) was added dropwise to the reaction and stirred for 18 h. The reaction was poured onto EtOAc and washed with aq. 10% $NaHSO_4$, sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (flash, SiO_2, 0% to 50% EtOAc/hexane) gave 360 mg (86%) of **607a** as a foam.

Step B. A solution of **607a** (360 mg) in 5 ml of CH_2Cl_2 was added dropwise to a suspension of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodioxol-3(1H)-one (362 mg, 0.85 mmol) in 20 ml of CH_2Cl_2. The reaction was stirred for 4.5 h, diluted with CH_2Cl_2 and washed with a 1:1 mixture of sat. aq. $NaHCO_3$/sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$ (2x) and sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (flash, SiO_2, 20% EtOAc/CH_2Cl_2) gave 340 mg (95%) of the ketone **608a**.

Step C. **608a** (300 mg, 0.36 mmol) was dissolved in 25 ml of 25% TFA/CH_2Cl_2 and stirred at RT for 5 h and concentrated *in vacuo*. Chromatography (flash, SiO_2, 0 to 5% MeOH/CH_2Cl_2) gave 118 mg (42%) of **609a** as a white solid: ^1H NMR (CD_3OD) δ 7.62-6.65 (16H, m), 4.85-4.7

(1H, m), 4.68-4.42 (2H, m), 4.40-4.15 (2H, m), 3.48-3.28 (1H, m), 3.0-2.9 (1H, m), 2.9-2.6 (4H, m), 2.55-2.18 (3H, m), 2.16-1.96 (2H, m).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609b) was prepared from **603d** in a similar manner as **609a** to give 287 mg (43% overall yield) as white solid: ^1H NMR(DMSO-d_6) δ 1.6(s, 3H), 2.7-3.1(m, 2H), 3.45(m, 1H), 4.4(t, 1H), 4.7(m, 2H), 4.95(m, 1H), 5.2, 5.4(2s, 1H), 7.2-7.65(m, 8H), 7.9(d, 2H), 8.8(t, 1H), 8.9,9.1(2s, 1H), 12.6(br, 1H).



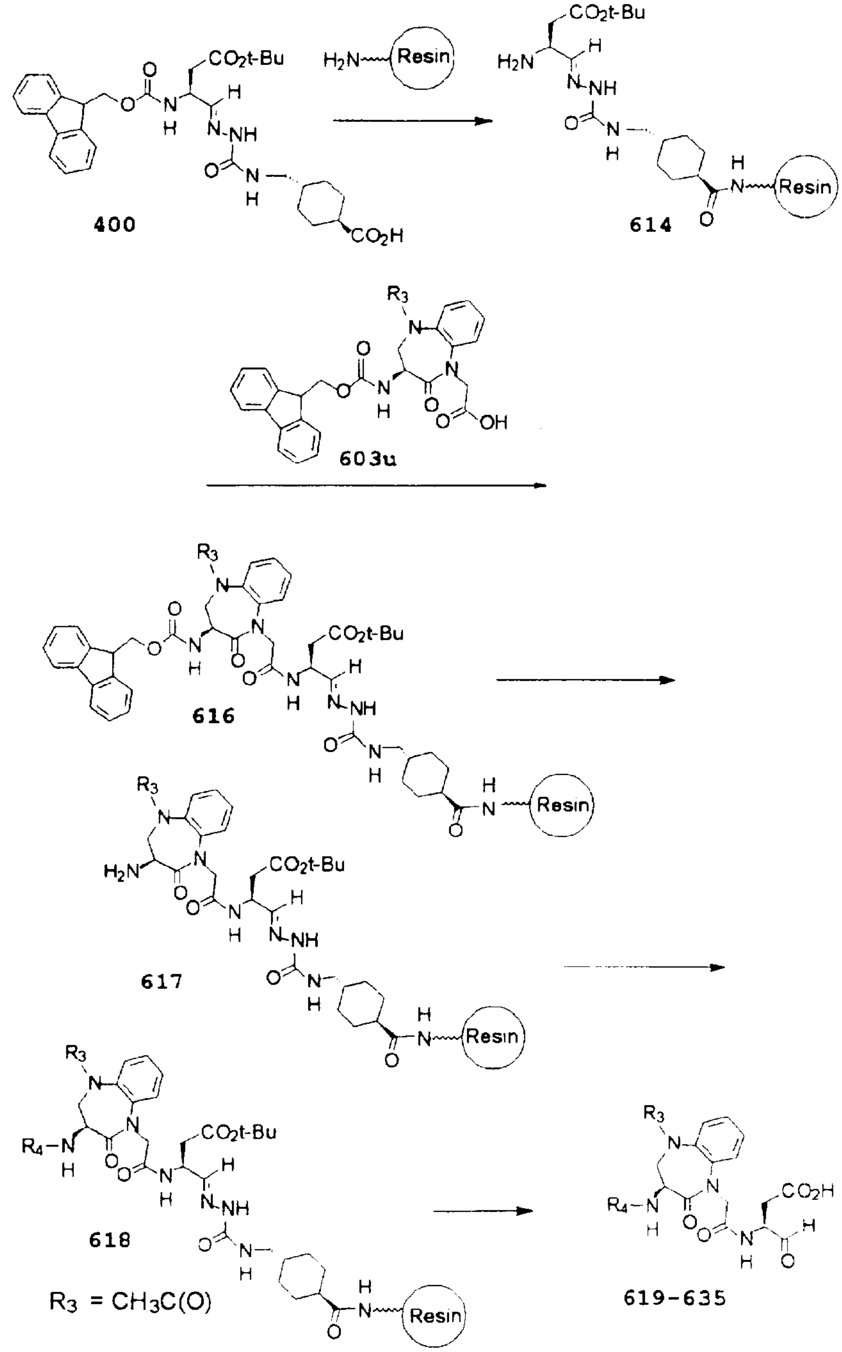
612

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-methanesulfonyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (612) was prepared by a method similar as **607a** (Steps A and C only) using **603m** (150 mg, 0.36 mmol)

instead of **603r** and (3*S*)-3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoic acid *t*-butyl ester (110; 160 mg, 0.36 mmol, WO 93/16710) instead of **606a** to give **612** (56%) as a white solid: ^1H NMR ($CDCl_3$) 7.85-7.10 (12H, m), 5.4-4.65 (4H, m), 4.6-4.15 (4H, m), 3.10-2.72 (5H, s & m).

Example 13

Compounds **619-635** were synthesized as described in Example 13 and Table 14.



400
614
603u
616
617
618
R3 = CH3C(O)
619-635

Syntheses of 619-635.

Step A. Synthesis of 614. TentaGel S® NH_2 resin (0.16 mmol/g, 10.0 g) was placed in a sintered glass funnel and washed with dimethylformamide (3 X 50 mL), 10% (v/v) diisopropylethylamine (DIEA) in dimethylformamide (2 X 50 mL) and finally with dimethylformamide (4 X 50 mL). Sufficient dimethylformamide was added to the resin to obtain a slurry followed by **400** (1.42 g, 2.4 mmol, prepared from (3S) 3-(fluorenylmethyloxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), 1-hydroxybenzotriazole hydrate (HOBT$\cdot H_2O$; 0.367 g, 2.4 mmol), O-benzotriazole-N,N,N,N'-tetramethyluronium hexafluorophosphate (HBTU; 0.91 g, 2.4 mmol), and DIEA (0.55 mL, 3.2 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin was isolated on a sintered glass funnel by suction filtration and washed with dimethylformamide (3 X 50 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) acetic anhydride/dimethylformamide (2 X 25 mL) directly in the funnel (10 min/wash). The resin was washed with dimethylformamide (3 X 50 mL) and dichloromethane (3 X 50 mL) prior to drying overnight *in vacuo* to yield **614** (11.0 g, quantitative yield).

Step B. Synthesis of 616. Resin **614** (3.0 g, 0.16 mmol/g, 0.48 mmol) was swelled in a sintered glass funnel by washing with dimethylformamide (3 X 15 mL). The Fmoc protecting group was then cleaved with 25% (v/v) piperidine/dimethylformamide (15 mL) for 10 min

(intermittent stirring) and then for 20 min with fresh piperidine reagent (15 ml). The resin was then washed with dimethylformamide (3 X 15 ml), followed by N-methypyrrolidone (2 X 15 mL). After transferring the resin to a 100 mL flask, N-methypyrrolidone was added to obtain a slurry followed by **603u** (0.736 g, 0.72 mmol), HOBT·H_2O (0.112 g, 0.73 mmol), HBTU (0.27 g, 0.73 mmol) and DIEA (0.26 mL, 1.5 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin work-up and capping with 20% (v/v) acetic anhydride in dimethylformamide were performed as described for **614** to yield **616** (3.13 g, quantitative yield).

Step C. Synthesis of 617. This compound was prepared from resin **616** (0.24 g, 0.038 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (3 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **617**. The resin was washed with dimethylformamide (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL).

Step D. Method 1. (624). Resin **617** was acylated with a solution of 0.4M thiophene-3-carboxylic acid and 0.4M HOBT in N-methypyrrolidone (1 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.35 mL) and the reaction was shaken for 2 hr at room temperature. The acylation step was repeated. Finally, the resin was washed with dimethylformamide (3 X 1 mL), dichloromethane (3 X 1 mL) and dried *in vacuo*.

The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H2O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 ether:pentane (12 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% acetonitrile/90% H2O/0.1% TFA (15 mL) and lyophilized to obtain crude **624** as a white powder. The compound was purified by semi-prep RP-HPLC with a Rainin Microsorb™ C18 column (5 u, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 45 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **624** (10.0 mg, 54%).

Step D. Method 1A. Synthesis of 627. Following a similar procedure as method 1, resin **617** was acylated with 4-(1-fluorenylmethoxycarbonylamino)benzoic acid and repeated. The Fmoc group was removed as described in Step C and the free amine was acetylated with 20% (v/v) acetic anhydride in dimethylformamide (1 mL) and 1.6M DIEA in N-methylpyrrolidone (0.35 mL) for 2 hr at room temperature. The acetylation step was repeated. Cleavage of the aldehyde from the resin gave **627** (4.2 mg, 20%).

Step D. Method 2. Synthesis of 632. Following a similar procedure as method 1, resin **617** was acylated with 0.5M cinnamoyl chloride in N-methypyrrolidone (1 mL) and 1.6M DIEA in N-methypyrrolidone (0.35 mL) for 2 hr at room temperature. The acylation step was

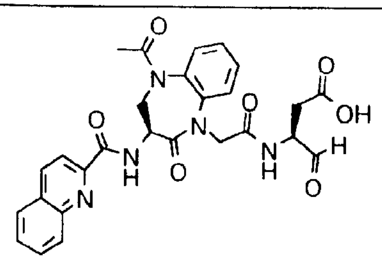
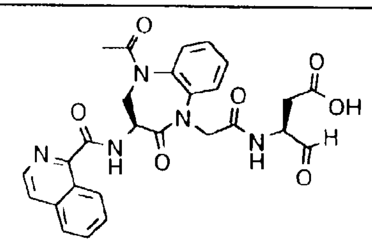
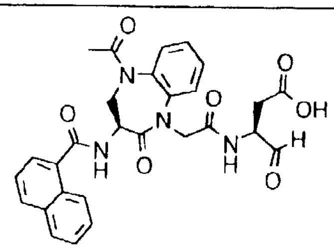
repeated. Cleavage of the aldehyde from the resin gave **632** (11.1 mg, 58%).

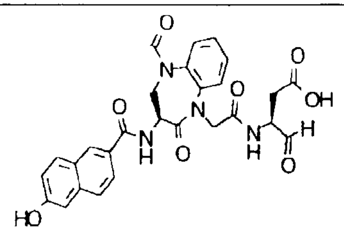
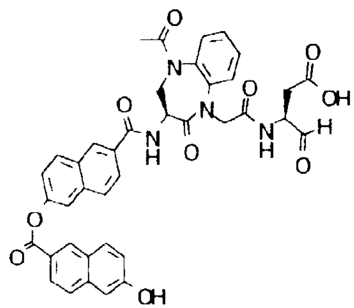
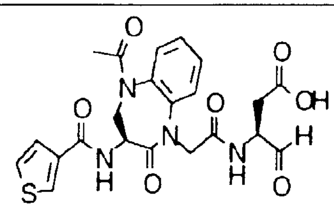
Step D. Method 3. Synthesis of 629. Following a similar procedure as method 1, resin **617** was reacted with 1.0M benzenesulfonyl chloride in dichloromethane (0.5 mL) and 1M pyridine in dichloromethane (0.60 mL) for 4 hr at room temperature. The reaction was repeated. Cleavage of the aldehyde from the resin **629** (4.7 mg, 24%).

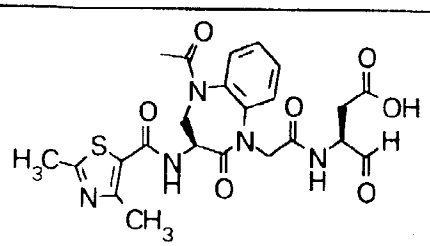
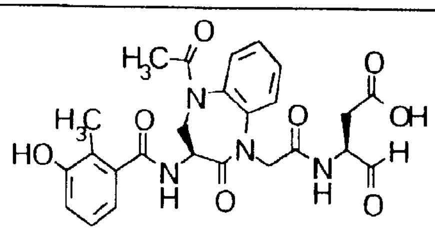
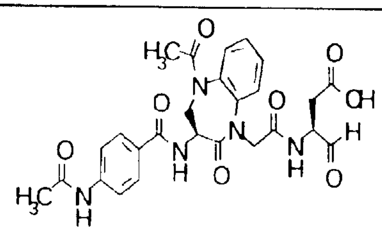
Analytical HPLC methods:

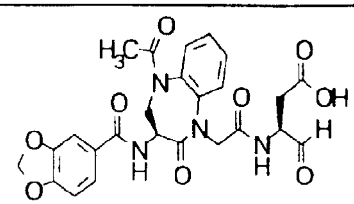
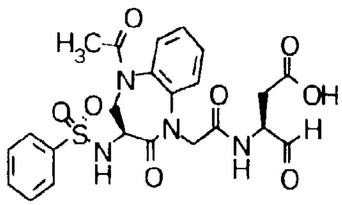
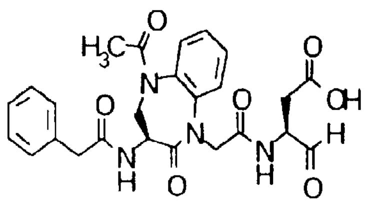
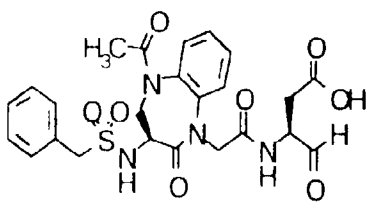
(1) Waters DeltaPak C18, 300A (5u, 3.9 X 150 mm). Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

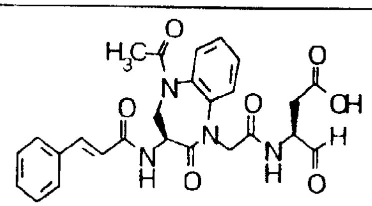
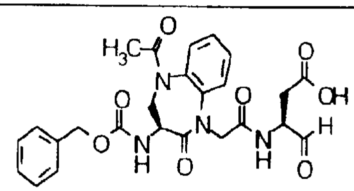
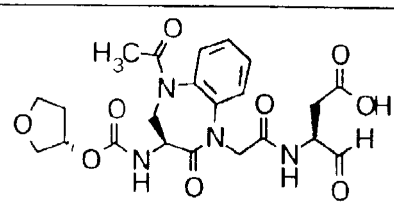
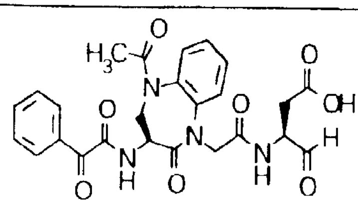
Table 14

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
619		C27H25N5O7	531.53	11.71 (1) 98%	532	1
620		C27H25N5O7	531.53	10.44 (1) 98%	532	1
621		C28H26N4O7	530.54	11.57 (1) 98%	(M+Na)+ 553	2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
622		C28H26N4O8	546.54	10.19 (1) 98%	(M+Na)+ 569	1
623		C39H32N4O10	716.71	15.8 (1) 09%	(M-) 716	1
624		C22H22N4O7S	486.51	8.39 (1) 98%	487	1

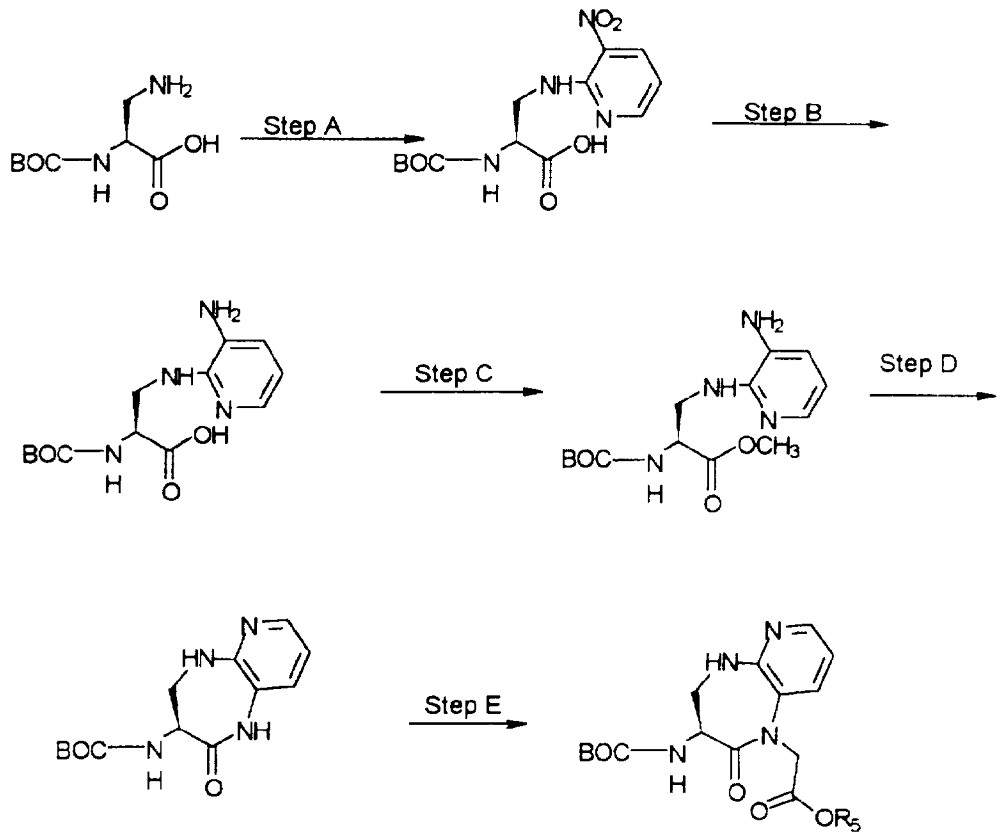
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
625		C23H25N5O7S	515.55	7.60 (1) 98%	516	1
626		C25H26N4O8	510.51	7.58 (1) 98%	511	1
627		C26H27N5O8	537.53	7.96 (1) 98%	538	1A

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
628		C25H24N4O9	524.49	9.50 (1) 98%	525	1
629		C23H24N4O8S	516.53	9.85 (1) 98%	517	3
630		C25H26N4O7	494.51	9.25 (1) 98%	495	2
631		C24H26N4O8S	530.56	10.19 (1) 98%	531	3

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
632		C26H26N4O7	506.52	10.99 (1) 98%	507	2
633		C25H26N4O8	510.51	11.48 (1) 98%	511	2
634		C22H26N4O9	490.47	6.87 (1) 98%	491	2
635		C25H24N4O8	508.49	10.03 (1) 98%	509	1

Example 14

Compounds **1605a-j**, **1605m**, **1605n**, **1605p**, **1605t**, and **1605v** were synthesized as described below.



1600 1601

(3*S*) N-(2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-pyrido [3,4-b][1,4-diazepine (1600).

Step A. (2*S*) 2-*tert*-Butoxycarbonylamino-3-(3-nitropyridin-2-ylamino)propionic acid was prepared by a similar method as (2S) 2-*tert*-butoxycarbonylamino-3-(2-nitrophenyl-amino)propionic acid in Step A of the synthesis of **600a/103**, except that 3-chloro-3-nitro pyridine was used instead of 2-

fluoronitrobenzene, to give 4.05 g (64%) of a yellow solid.

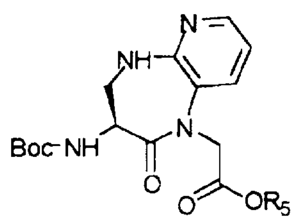
Step B. (2*S*) 2-*tert*-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid was prepared by a similar method to (2*S*) 2-*tert*-Butoxycarbonylamino-3-(2-aminophenylamino)-propionic acid in Step B of the synthesis of **600a/103** to give 3.68 g (quant.) as a dark solid.

Step C. (2S) 2-*tert*-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid methyl ester. A solution of (2S) 2-*tert*-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)-propionic acid (360 mg, 1.21 mmol) and MeOH (59 mg, 1.82 mmol) in anhydrous CH_2Cl_2 (20 ml) was treated with 4-dimethylaminopyridine (DMAP, 163 mg, 1.33 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (280 mg, 1.45 mmol). The reaction was stirred for 18 h, diluted with EtOAc (150ml), washed with water (2x), sat. aq. $NaHCO_3$, and sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (flash, SiO_2, 0 to 5% MeOH/CH_2Cl_2) gave 250 mg (67%) of the title compound as a light tan solid.

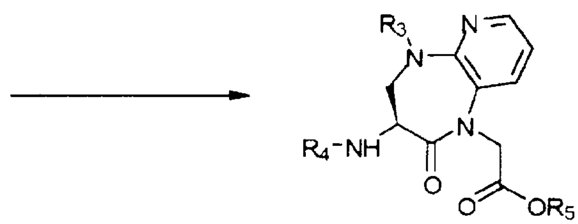
Step D. (3S) N-(2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1H- pyrido[3,4-b][1,4-diazepine (1600). A solution of (2S) 2-*tert*-butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid methyl ester (70 mg, 0.225 mol) and 25% sodium methoxide/MeOH (130 µl, 0.56 mmol) in anhydrous MeOH (4 ml) was heated at 60°C for 16 h.

The reaction was concentrated *in vacuo*, the residue dissolved in 2 ml of H_2O and extracted with EtOAc (3x). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (flash, SiO_2, 0 to 3% $MeOH/CH_2Cl_2$) gave 7.5 mg (3%) of **1600** as a light tan solid: ^1H NMR (CD_3OD) δ 7.96-7.92 (1H, d), 7.75-7.65 (1H, br. s), 7.14-7.08 (1H, d), 6.73-6.65 (1H, m), 5.83-5.75 (1H, br. s), 5.4-5.25 (1H, br. s), 4.6-4.5 (1H,m), 3.95-3.84 (1H, m), 3.55-3.48 (1H, m), 1.4 (9H, s)

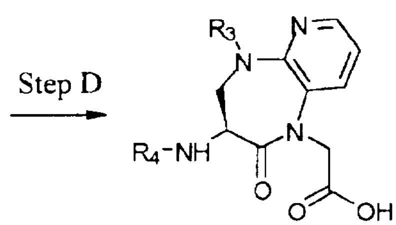
Step E. **1601** is prepared from **1600** following the method in Step D for the preparation **600a/103**.



1601

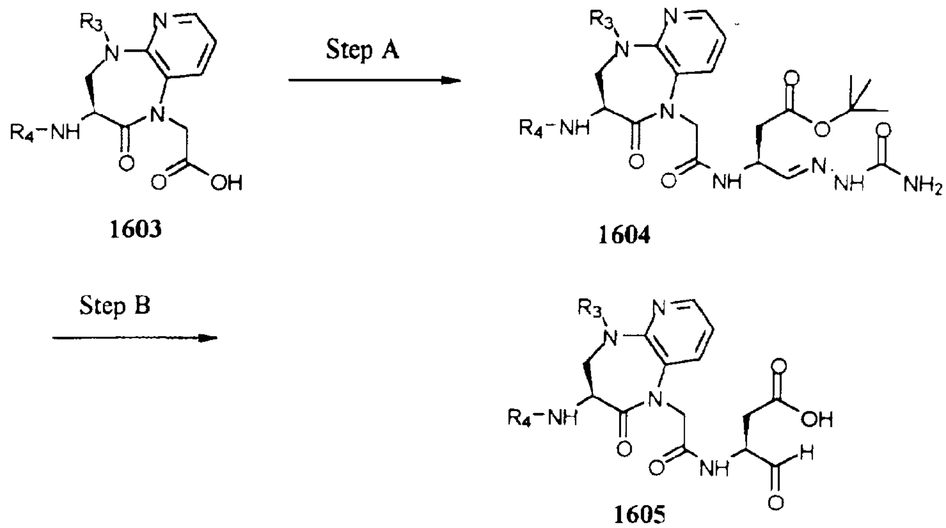


1602



1603

Synthesis of 1603. **1603** is prepared from **1601** following the methods for the synthesis of **603** from **600**.



Synthesis of 1605. **1605** is prepared from **1603** by methods described for the synthesis of **605** from **603**.

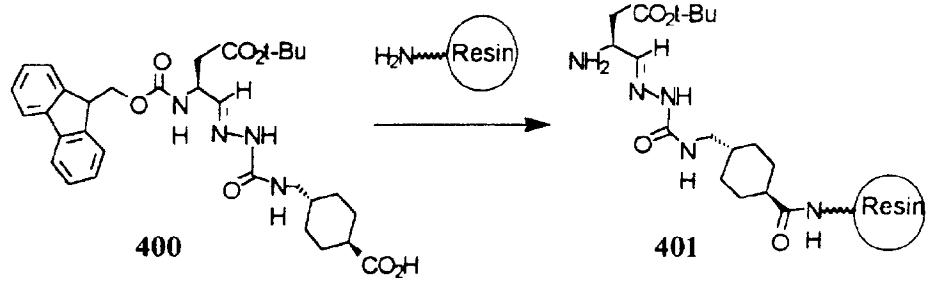
<u>**Table 15**</u>

1605	R_3	R_4
a	$PhCH_2CH_2CO$	PhCO
b	$PhCH_2CO$	PhCO
c	PhCO	PhCO
d	CH_3CO	PhCO
e	CH_3OCH_2CO	PhCO
f	$(CH_3)_2CHCH_2CO$	PhCO
g	CH_3COCH_2CO	PhCO
h	CH_3OCOCO	PhCO
i	CH_3COCO	PhCO
j	CH_3OCO	PhCO
m	CH_3SO_3	PhCO
n	CH_3CO	Naphthyl-2-CO
p	$PhCH_2NHCO$	PhCO

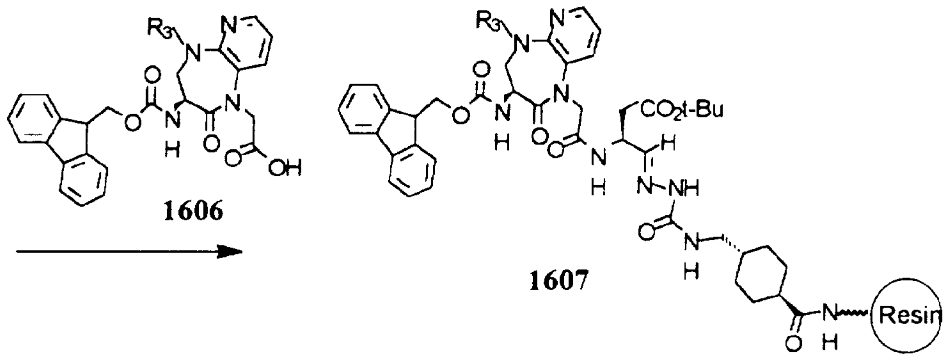
t	3-CH_3PhCH_2CO	PhCO
v	$PhCH_2CH_2CO$	$PhCH_2$

Example 15

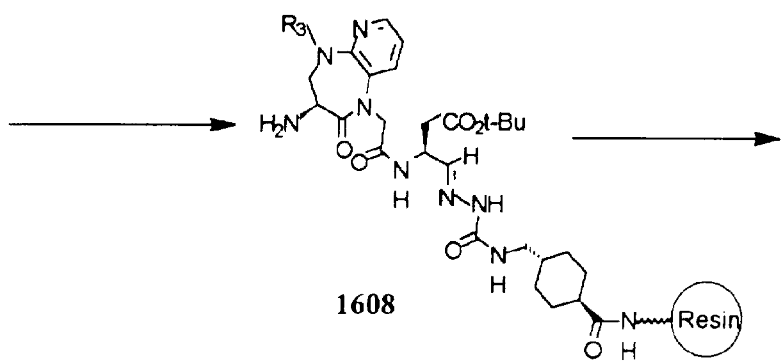
Compounds **1610-1621** are prepared from **1600** by methods similar to the methods used to prepare compounds **619-635** from **600a/103** and **600b**.



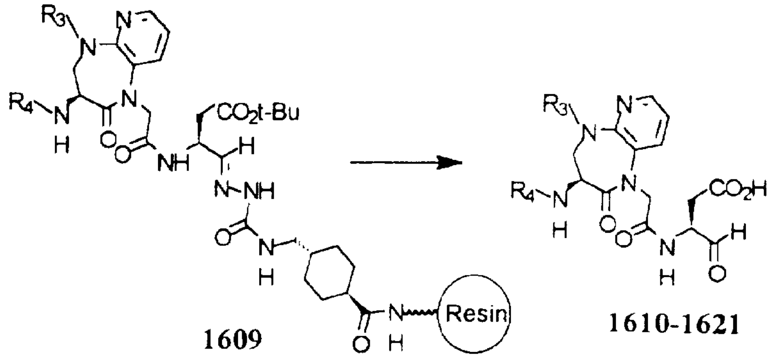
400 401



1606 1607



1608

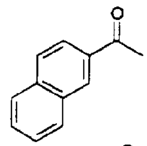


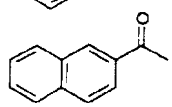
1609 1610-1621

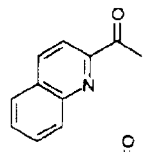
wherein for compounds **1610-1621**,

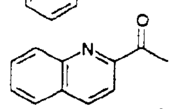
a R_3 = $CH_3C(O)$-
b R_3 = $CH_3OCH_2C(O)$-:

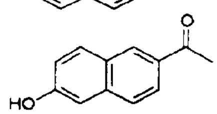
<u>R_4</u>

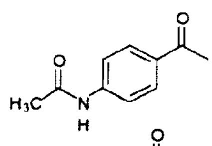
1610 

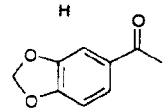
1611 

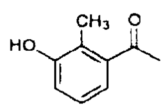
1612 

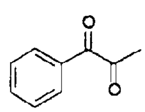
1613 

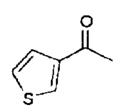
1614 

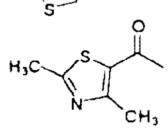
1615 

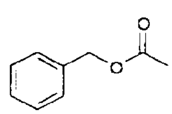
1616 

1617 

1618 

1619 

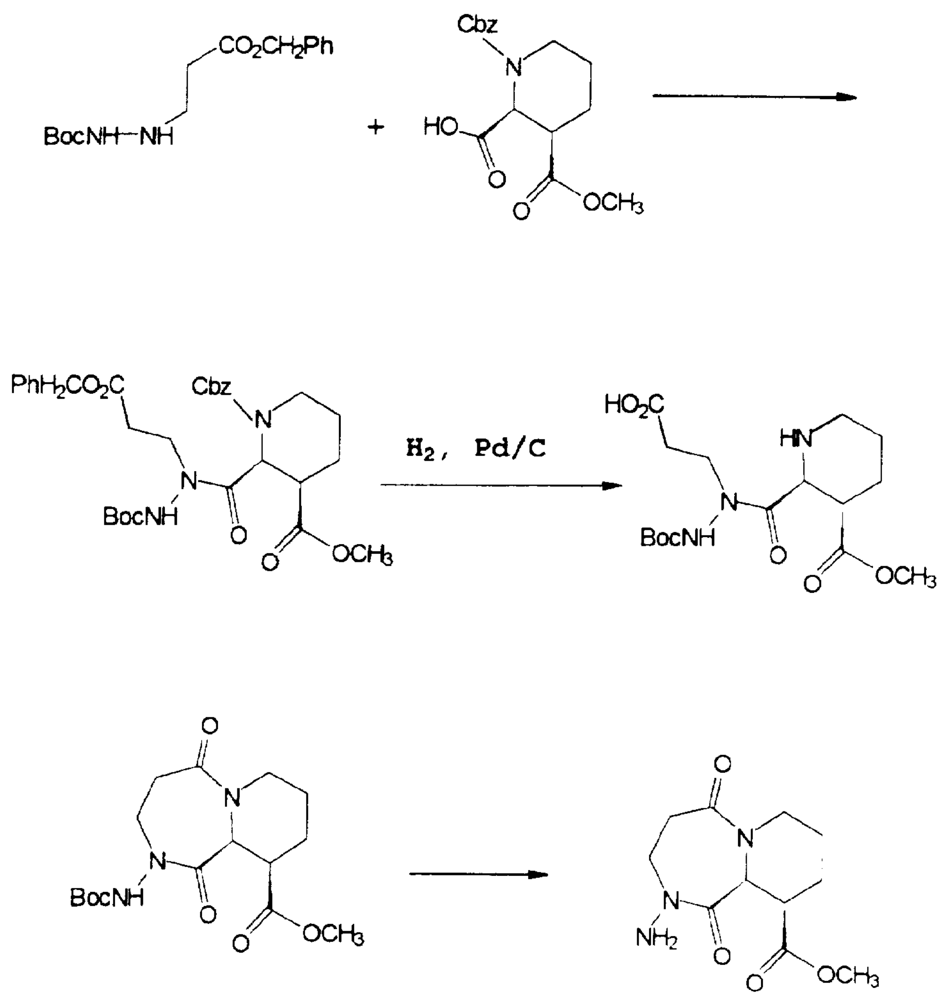
1620 

1621 

Example 16

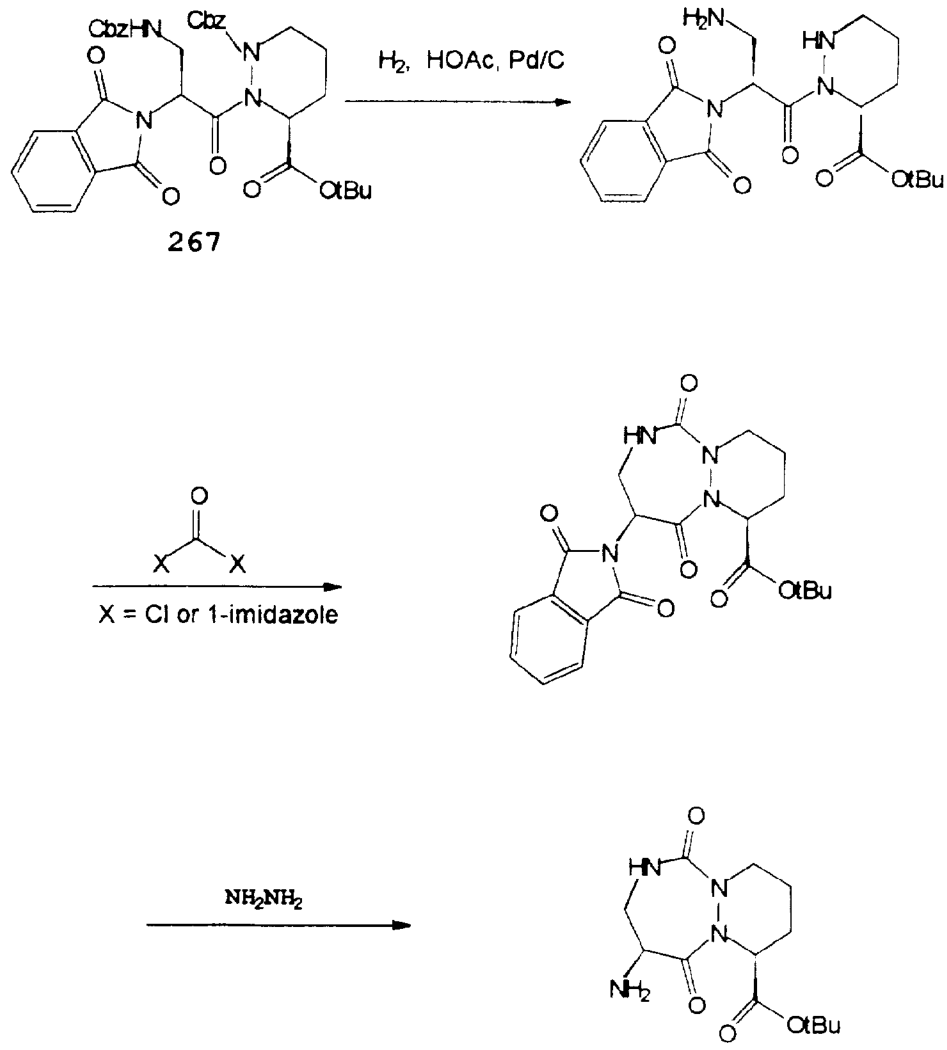
Compounds comprising scaffolds (e11), (y1), (y2), (z), and (e12) may be synthesized as described below.

Synthesis of Scaffold R_1, wherein R_1 is (e11) and wherein Y_2 is =O.



269

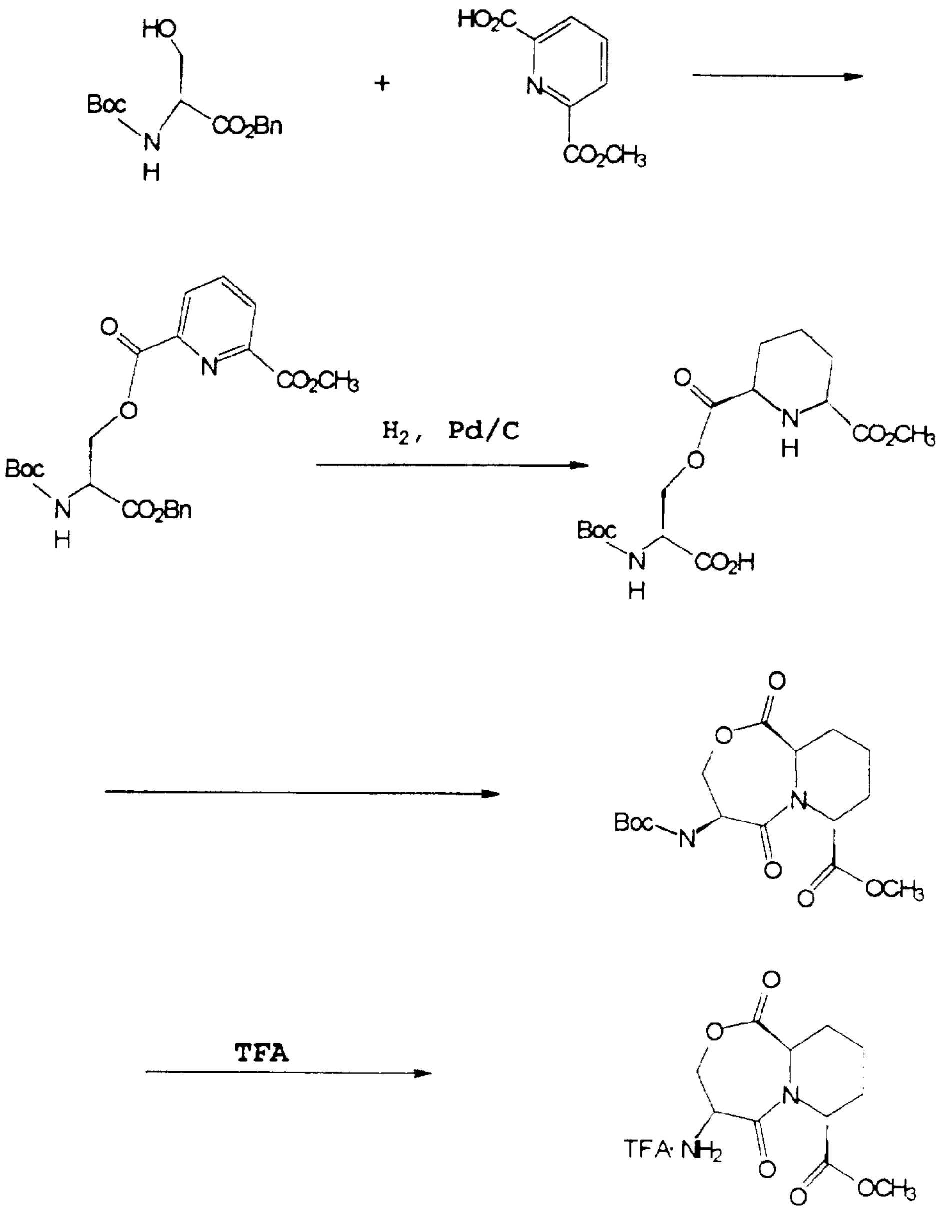
Synthesis of Scaffold R_1, wherein R_1 is (y1) and wherein Y_2 is =O.



267

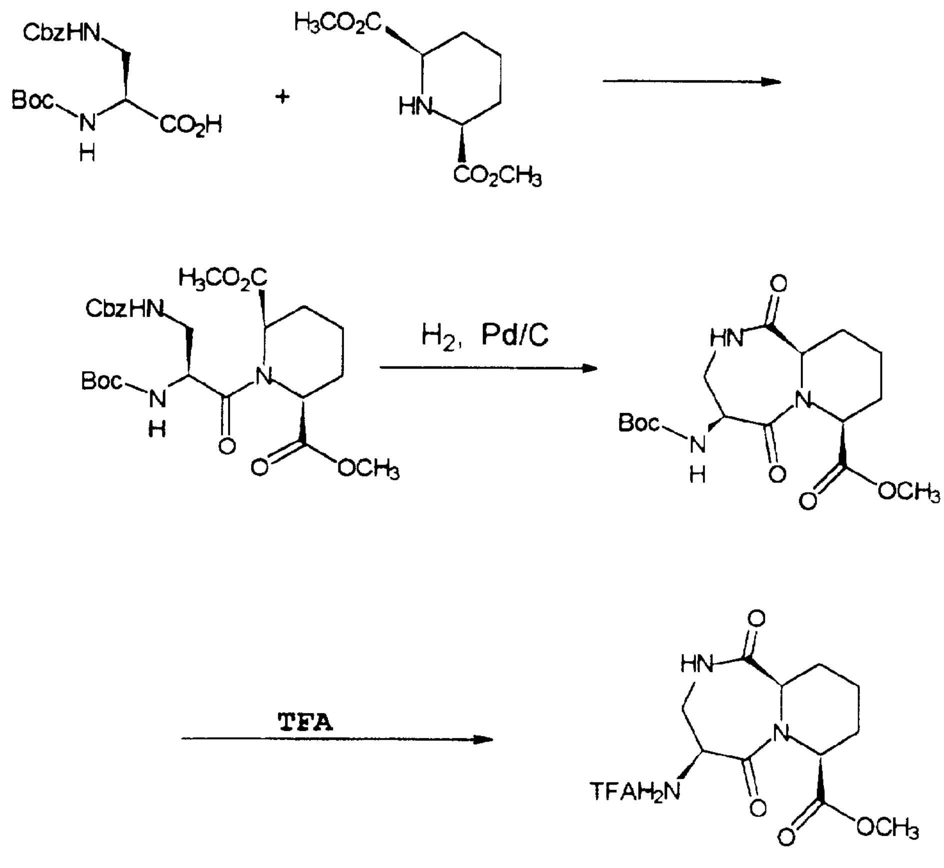
270

Synthesis of Scaffold R_1, wherein R_1 is (y2) and wherein Y_2 is H_2 and X_7 is O.



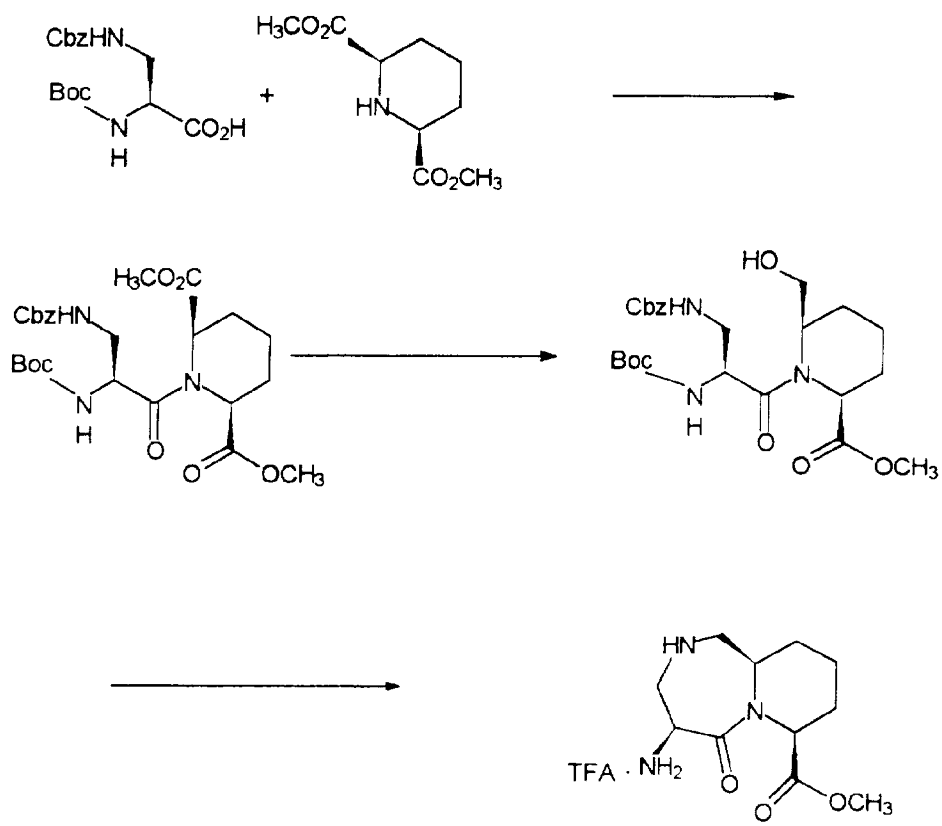
273

Synthesis of Scaffold R_1, wherein R_1 is (y2) and wherein Y_2 is =0 and X_7 is NH.



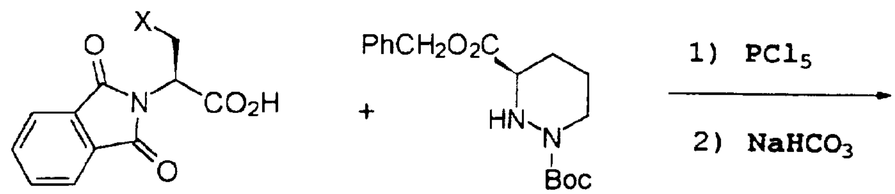
271

Synthesis of Scaffold R_1, wherein R_1 is (y2) and wherein Y_2 is H_2 and X_7 is NH.

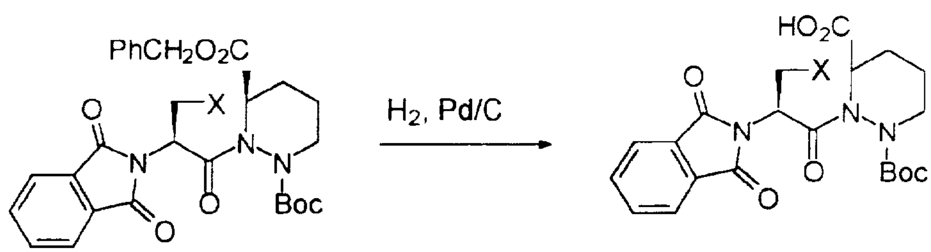


272

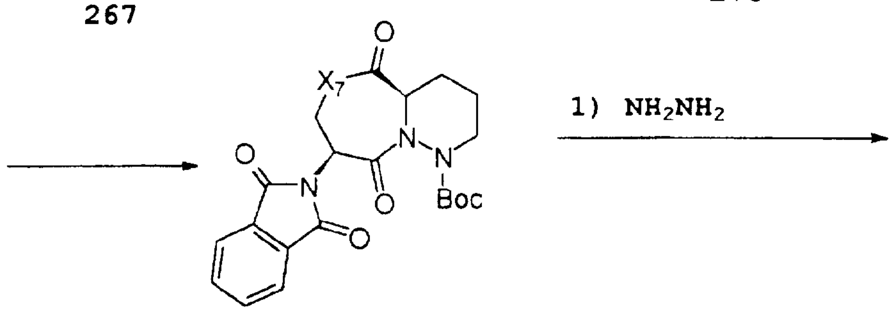
Synthesis of Scaffold R_1, wherein R_1 is (z) and wherein Y_2 is O.

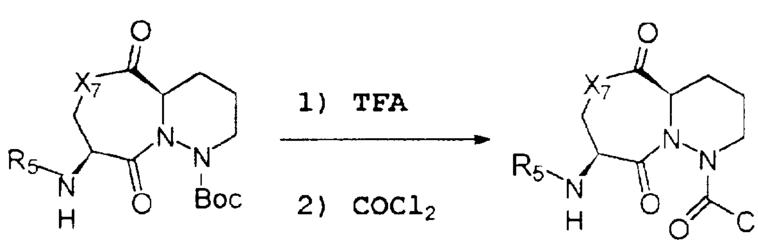


X = NHCbz
X = OCH_2Ph



267 270

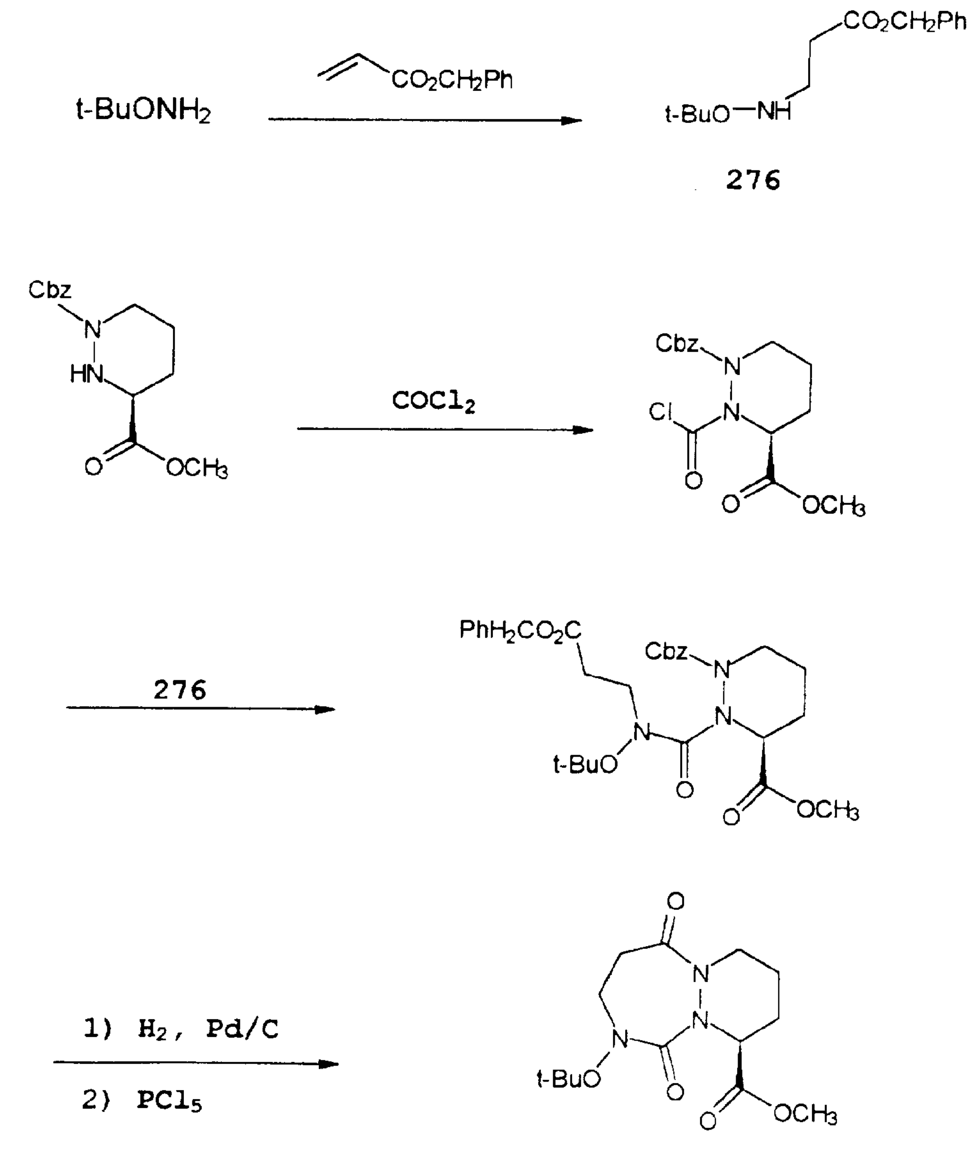




271

274 X_7 = NH
275 X_7 = O

Synthesis of Scaffold R_1, wherein R_1 is (e12) and wherein Y_2 is =0.



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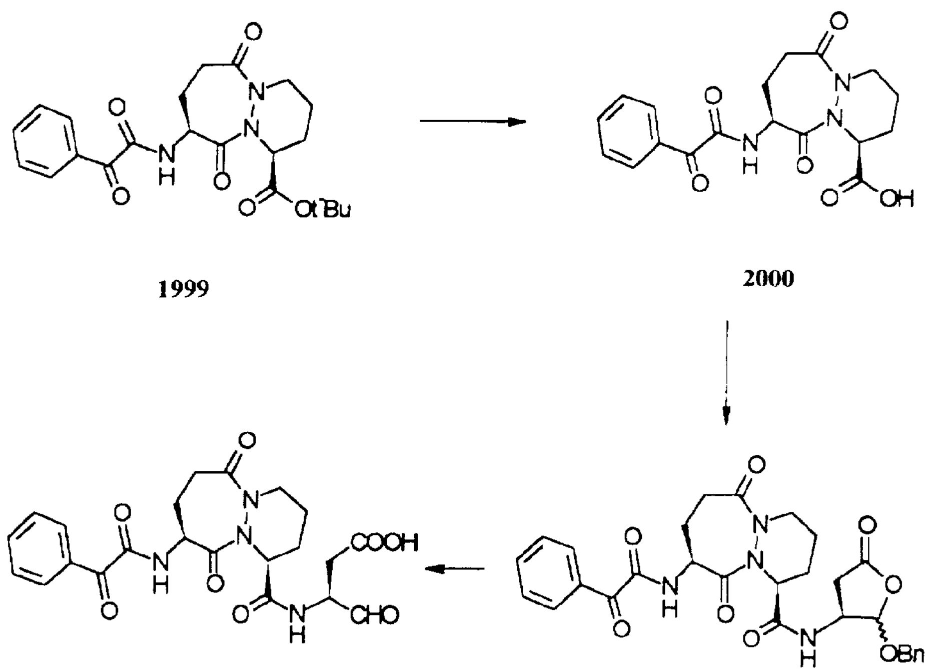
Example 17

The preparation of compounds **2001**, **2002**, **2100a-e**, and **2201** is described below.



1999 2000 2001 2002

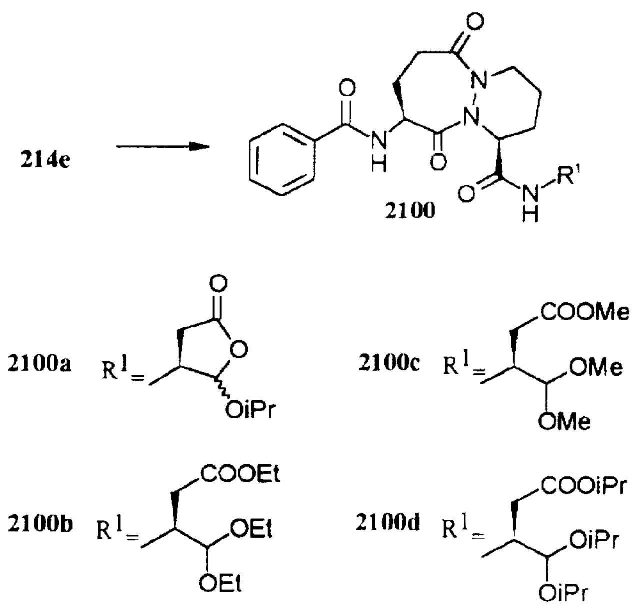
(1*S*,9*S*) 9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a]-[1,2] diazepine-1-carboxylic acid (2000). To a solution of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 340 mg, 1.15 mmol) in CH_2Cl_2 was added benzoylformic acid (260 mg, 1.7 mmol), HOBT (230 mg, 1.7 mmol) and EDC (340 mg, 1.7 mmol). The resulting mixture was stirred at ambient temperature for 16 hours, poured into 1N HCl and extracted with CH_2Cl_2. The organic extracts were

further washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to afford **1999** as a pale yellow solid. The solid was dissolved in CH_2Cl_2 (25 ml) and TFA (25 ml) and stirred overnight and concentrated in vacuo to give 560 mg of **2000** as an oil.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2(*R*,*S*)-benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamide (2001), was synthesized from **2000** by methods similar to compound **213e** to afford 410 mg (63%) of **2001** as a white solid: ^1H NMR ($CDCl_3$; mixture of diastereomers) δ 8.25 (1H, d), 8.23 (1H, d), 7.78 (1H, dd), 7.65 (1H, bm), 7.50 (2H, m), 7.40-7.25 (4H, m), 6.55 (1H, d), 5.57 (1H, d), 5.10 (1H, t), 5.05-4.95 (2H, m), 4.90, (1H, d), 4.80 (1H, d), 4.72 (1H, bm), 4.65 (1H, m), 4.55 (1H, m), 4.45 (1H, t), 3.25 (1H, m), 3.15 (1H, m), 3.00 (2H, bm), 2,90 (1H, dd), 2.70 (1H, m), 2.47 (1H, dd), 2.45 (1H, m), 2.35 (1H, m), 2.00-1.75 (4H, m), 1.60 (1H, bm).

[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4-oxobutanoic acid (2002). Compound **2001** (58.6 mg, 0.10 mmol) was treated with 15 ml of TFA/MeCN/water (1:2:3) and stirred at room temperature for 6.5 h. The reaction was extracted with ether. The aqueous layer was concentrated with azeotropic removal of the water using MeCN. The product was suspended in CH_2Cl_2, concentrated in vacuo and precipitated with ether to give 46.8 mg

(99%) of **2002** as a white solid: ^{1}H NMR (CD_3OD) δ 9.05 (0.25H, d), 8.15 (1H, d), 7.68 (1H, t), 7.64 (0.25H, d), 7.55 (3H, t), 7.35 (0.5H, m), 5.22 (1H, t), 4.90 (1H, m), 4.58 (1H, dd), 4.50 (1H, m), 4.28 (1H, bm), 3.45 (1H, m), 3.10 (1H, bt), 2.68 (1H, ddd), 2.60-2.45 (2H, m), 2.30 (1H, dd), 2.15-2.05 (2H, m), 1.90 (2H, bm), 1.68 (1H, bm).



[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-isopropoxy-5-oxo-tetrahydro-furan-3-yl)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamide (2100a). A solution of **214e** (101 mg, 0.23 mmol) in isopropanol (10 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (10 mg). After 75 minutes, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and

concentrated. Flash chromatography (SiO_2, CH_2Cl_2 to EtOAc) afforded 56 mg (51%) of **2100a** as a white solid: ^1H NMR ($CDCl_3$; mixture of diastereomers) δ 7.9-7.8 (2H,m), 7.6-7.5 (1H, m), 7.5-7.4 (2H, m), 7.1 (0.5H, d), 6.9 (0.5H, d), 6.4 (0.5H,d), 5.6 (0.5H, d), 5.3 (0,5H, s), 5.2-5.1 (1H, m), 4.95 (0.5H, m), 4.75-4.5 (1.5H, m), 4.35 (0.5H, t), 4.1 (0.5H, m), 3.98 (0.5H, m), 3.3-2.75 (4H, m), 2.5-2.4 (2H,m), 2.25 (1H, m), 2.1-1.9 (3H,m) 1.75-1.55 (2H,m).

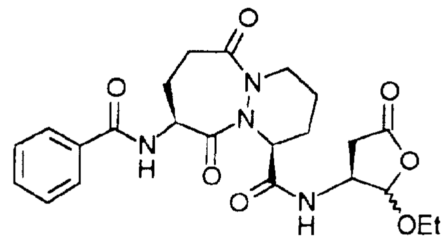
[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-diethoxy-butyric acid, ethyl ester (2100b). A solution of **214e** (16 mg, 0.036 mmol) in ethanol (2 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (2 mg). After 5 days, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated. Flash chromatography (SiO_2, CH_2Cl_2:EtOAc 95:5 v/v) afforded 16 mg (81%) of **2100b** as a white solid: ^1H NMR ($CDCl_3$) d 7.85-7.74 (2H,m), 7.55-7.38 (3H,m), 7.04-6.95 (1H,d), 6.61-6.48 (1H,d), 5.15-5.08 (1H,m), 4.63-4.53 (1H,m), 4.52-4.45 (1H,m), 4.42-4.35 (1H,m), 4.15-4.05 (2H,m), 3.74-3.60 (2H,m), 3.57-3.42 (2H,m), 3.39-3.28 (1H,m), 3.03-2.93 (1H,m), 2.92-2.82 (1H,m), 2.65-2.52 (2H,m), 2.42-2.25 (1H,m), 2.20-1.88 (4H,m), 1.76-1.50 (2H,m), 1.35-1.10 (9H,m).

[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-dimethoxy-butyric acid

methyl ester (2100c). A solution of **214e** (165 mg, 0.37 mmol) in methanol (5 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (17.5 mg). After 4 days, the reaction mixture was diluted with EtOAc and washed with 10% $NaHCO_3$ (3x) and brine. The combined extracts were dried over Na_2SO_4 and concentrated. Flash chromatography (SiO_2, EtOAc) afforded 127 mg (68%) of **2100c** as a white solid: ^1H NMR ($CDCl_3$) δ 7.82 (2H, d), 7.55-7.50 (1H, m), 7.47-7.43 (2H, m), 7.02 (1H, d), 6.53 (1H, d), 5.20-5.10 (1H, m), 4.56-4.50 (1H, m), 4.45-4.50 (1H each, two m), 3.69 (3H, s), 3.41 (3H, s), 3.43 (3H, s), 3.35-3.25 (1H, m), 3.06-2.98 (1H, m), 2.94-2.83 (1H, m), 2.65-2.53 (2H, m), 2.35-2.32 (1H, m), 2.15-2.07 (1H,m), 2.00-1.89 (3H, m), 1.75-1.56 (2H, m).

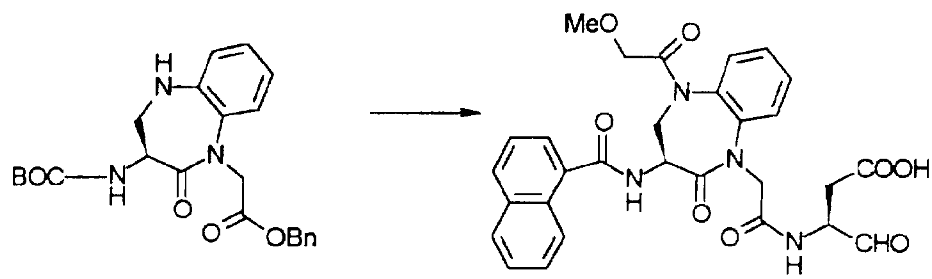
[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-diisopropoxy-butyric acid, isopropyl ester (2100d). A solution of **214e** (53 mg, 0.12 mmol) in isopropanol (5 ml) was stirred at 50 °C with a catalytic amount of *p*-toluenesulfonic acid (5 mg). After 3 days the reaction mixture was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated. Flash chromatography (SiO_2, CH_2Cl_2:EtOAc (4:1 to 1:1 v/v)) afforded 49 mg (68%) of **2100d** as a white solid: ^1H NMR ($CDCl_3$) δ 7.85 (2H, d), 7.50-7.43 (1H, m), 7.41-7.35 (2H, m), 7.02 (1H, d), 6.47 (1H, d), 5.13-5.07 (1H, m) 5.00-4.9 (1H, m), 4.61-4.55 (2H, m), 4.37-4.30(1H, m), 3.80-3.70 (1H, m), 3.90-3.80 (1H, m), 3.42-3.35 (1H, m),

3.03-2.93 (1H, m), 2.91-2.81 (1H, m), 2.62-2.50 (2H, m), 2.38-2.33 (1H, m), 2.12-2.06 (1H,m), 1.97-1.81 (3H, m), 1.70-1.60 (2H, m), 1.28-1.05 (18H,m).



2100e

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxo-tetrahydro-furan-3-yl)-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamide (2100e), was synthesized from **302** via methods used to synthesize **304a** to afford **2100e**, except ethanol and triethylorthoformate were used instead of methanol and trimethylorthoformate. Chromatography (SiO_2, 5% ethanol/CH_2Cl_2) afforded 92 mg (68%) of a white solid: ^1H NMR ($CDCl_3$; mixture of diastereomers) δ 7.90-7.80 (2H, m), 7.60-7.50 (1H, m), 7.50-7.40 (2H, m), 7.30 (0.5H, d), 7.00 (0.5H, d), 6.50 (0.5H, d), 5.50 (0.5H, d), 5.20-5.10 (1.5H, m), 4.95 (0.5H, m), 4.75-4.65 (0.5H, m), 4.65-4.50 (1H, m), 4.38 (0.05H, t), 4.00-3.90 (0.5H, m), 3.85-3.75 (0.5H, m), 3.75-3.65 (0.5H, m), 3.65-3.55 (0.5H, m), 3.30-2.70 (4H, m), 2.50-2.35 (2H, m), 2.30 (1H, d), 2.15-1.90 (3H, m), 1.80-1.60 (2H, m), 1.25-1.20 (3H, two t)



600b

2201

(3*S*)-3-[(3*S*)-2-oxo-3-(1-naphthoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (2201) was synthesized from **600b** by the methods used to synthesize **605b** to afford **2201**: ^{1}H NMR ($CDCl_3$) δ 8.30-8.22 (1H,m), 8.05-7.98 (1H, d), 7.96-7.83 (1H,m), 7.77-7.68 (1H,m), 7.67-7.40 (7H,m), 5.12-5.02 (1H,m), 4.98-4.41 (5H,m), 4.38-4.24 (1H,m), 4.07-4.00 (1H,d), 3.92-3.80 (2H,m), 3.32 (3H,s), 2.75-2.60 (1H,m), 2.58-2.35 (1H,m).

Example 18

We obtained the following data for selected compounds of this invention using the methods described herein (Table 16, see Example 7; Tables 17 and 18, see Examples 1-4). The structures and preparations of compounds of this invention are described in Examples 28-31.

Table 16 Comparison of Prodrugs for Efficacy in LPS Challenged Mice: Inhibition of IL-1β Production. The percent inhibition of IL-1β production after treatment with a compound of the invention is shown as a function of time after LPS challenge ("-" indicates that no value was obtained at that relative time).

	Time of Compound Administration (relative to time of LPS challenge, PO, 50 mg/kg)			
Compound	**-2h**	**-1h**	**0h**	**+1h**
213f	(-4)	-	8	-
213h	9	-	53	-
213i	(-11)	-	62	-
213k	0	-	68	-
213l	(-18)	-	80	-
213m	26	-	42	-
213o	4	-	8	-
213p	21	-	29	-
213q	17	-	91	-
213r	59	-	37	-
213x	0	-	78	-
213y	29	-	50	-
214e	39 43 -	- 44 -	70 48 -	75 11 47
214k	12	-	31	-
214l	0	-	54	-
214m	0	-	17	-
214w	11	-	91	-
264l	0	-	23	-
404	- 55	- -	- 6	56 -

Compound	-2h	-1h	0h	+1h
412	0	-	0	-
	11	-	37	-
418	-	-	-	64
	25	-	52	-
434	-	-	-	80
	0	-	63	-
450	0	-	35	-
452	-	-	-	70
	28	-	89	-
456	-	-	-	56
	41	-	69	-
470	0	-	36	-
471	0	-	34	-
475	0	-	15	-
481	27	-	0	-
486	19	-	15	-
487	17	-	20	-
528	25	-	67	-
550f	0	-	50	-
550h	55	-	73	-
550i	(-10)	-	23	-
550k	36	-	34	-
550l	9	-	38	-
550m	45	-	52	-
550n	19	-	65	-
550o	19	-	64	-
550p	30	-	60	-
655	0	-	68	-
656	31	-	16	-
662	41	-	75	-
668	-	-	-	53
695a	49	-	78	-
1015	15	-	28	-
2001	64	62	58	55
2001a	10	-	16	-
2002	5	-	87	-
2100h	34	-	32	-
2100i	19	-	74	-
2100j	48	41	0	33
2100k	30	50	32	72
2100l	52	-	28	-
2100m	40	-	42	-
2100n	21	9	64	73
2100o	31	44	68	64

Table 17 Data for selected compounds of this invention obtained using the methods described in Examples 1-4.

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50(nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
213f			3000		
213g			2200		
213h			1500		
213i			1100		
213j					
213k			2000		
213l			2000		
213m			2500		
213o		5000	3300		
213p			<300		
213q			<300		
213r			<300		
213v	0.5	1,100	1100	41	23
213x		4500	2500		
213y			930		
214j	4.2	2500	6000		
214k	0.2	500	580		22
214l	6	1900	1100		12
214m	1.5	530	2200		33.4
214w	0.6	620	370		15
246b	30000	>30000		87	
264l			3000		
265a	2600	25000			
265c	1100	4500			32
265d	500	1500			35
265f	1200				24
280b		13000			
280c		10000			86
280d		25000			
283b		1750			41
283c		4000			50

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
283d		>8000	10000		
308c	3000				
308d	3000				
500	25	1800	1800		
501	2.5	1800	1600		
505c		1500			
505d		>20000			
505f		550			
510a	65	200		267	
510d	2300	>20000			
511c	730	>20000		78	40
528			2200		
550f			1100		
550h			1800		
550i			1400		
550k			3000		
550l			750		
550m			2000		
550n			<300		
550o		450	3000		
550p			2900		
550q			700		
640	155	2250	3900		
642	35	8000	2900		
645	150				
650	550	4000			
653	30	2300	6000		
655					
656	0.6	2100	1600		2.9
662	0.5	1800	800		2.75
668	9	5200	3700		29
669	14		10000		
670			4500		
671	5	2000	2500		33.2
677			610		
678	5	2700	2200		
680					

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
681	9	3000	5000		
682			1300		
683	400	>20000	>20000		
684	15	5000	2800		
686	4	4000	9000		
688a			3000		
688b			1300		
689a	0.8	910	2500		
689b	2.2	600	2000		
690a			1600		
690b					
691a	2.1	2900	1200		9.9
691b	11.5	1,900	1400		
692a					
692b			1800		
693					
694	3	2600	2100		
695a					
695b					
695c			2500		
696	4.5	2000	2900		13
700	275				
701	90				
702	45	>5000	20000		
703	5	1400	20000		
704	30	2600	9800		
705	5	2300	3200		
706	5	2400	5800		
707	180				
708	140				
709	10	2100	14000		
710	110				
711	175				
910	10	3400	3800		
911	9	3500	1900		
912	10	4200	3800		
913	4.5	2400	7000		

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
914	5.2	2600	2800		
915	11.5	>8000	1900		
918	7		1150		
919	4	2000	4300		
920	16	2100	3000		
921	8.5	1800	3000		
1018	170	4000	5500		9.1
1052	100	2500			16
1053	27	2000	>20000		34
1056	170				17
1075	120	5000	5500		14.5
1095	360	6000			28
1105	250	3500	3000		
1106	75	4000	1700		
1107	65				
1108	22	1400	2600		
1109	80				
1110	45				
1111	18	6050	4400		
1112	3.5	1800	2300		
1113	290				
1114	125				
1115	250				
1116	215				
1117	35	1700	1300		
1118	380				
1119	515				
1120	95				
1121	170				
1122	400				
1123	30	2,400	4500		
1124	270				
1125	55	2300	9000		
2001a			3000		
2100f					
2100g					
2100h			2000		

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
2100i					
2100j	30000		12000		
2100k	520	4000	600		
2100l		750	2200		
2100m					
2100n	670	770	4000		
2100o	670	1150	1500		

We obtained the following data for selected compounds of this invention (Table 18) using the methods described herein (see Examples 1-4). The structures and preparations of compounds of this invention are described in Examples 28-31.

<u>Table 18</u>

Cmpd.	Fluorescent Assay k_{inact} m^{-1} s^{-1}	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
286	370000	300	1600		119
505 b	190000	1500	2100	161	196
505 e	420000	9000	1000		

<u>Example 19</u>

<u>In vivo acute assay for efficacy as anti-inflammatory agent</u>

Results in the Table 19 show that **412f**, **412d** and **696a** inhibit IL-1β production in LPS-challenged mice after oral adminstration using ethanol/PEG/water,

β-cyclodextrin, labrosol/water or cremophor/water as vehicles. The compound was dosed at time of LPS challenge. The protocol is described in Example 7.

Table 19 Inhibition (%) of IL-1β production in LPS-challenged mice.

Compound	10 mg/kg dose	25 mg/kg dose	50 mg/kg dose
412f	17%	25%	32%
412e	5%	17%	61%
696a	0	45%	52%

Example 20
Mouse Carrageenan Peritoneal Inflammation

Inflammation was induced in mice with an intraperitoneal (IP) injection of 10 mg carrageenan in 0.5 ml of saline (Griswold et al., Inflammation, 13, pp. 727-739 (1989)). Drugs are administered by oral gavage in ethanol/PEG/water, β-cyclodextrin, labrosol/water or cremophor/water vehicle. The mice are sacrificed at 4 hours post carrageenan administration, then injected IP with 2 ml of saline containing 5U/ml heparin. After gentle massage of the peritoneum, a small incision is made, the contents collected and volume recorded. Samples are kept on ice until centrifuged (130 x g, 8 mins at 4 °C) to remove cellular material, and the resultant supernatant stored at -20 °C. IL-1β levels in the peritoneal fluid are determined by ELISA.

Results in the Table 20 show prodrug **412f** inhibits IL-1β production in carrageenan-challenged mice after oral adminstration of drug. Compound **214e**

did not inhibit IL-1β production when dosed orally at 50 mg/kg.

Table 20 Inhibition (%) of IL-1β production by **412f** and **412d** in carrageenan-challenged mice.

Dose (mg/kg)	Compound **412f**	Compound **412d**
1	30%	0
10	54%	32%
25	49%	31%
50	73%	36%
100	75%	53%

Example 21

Type II Collagen-induced Arthritis

Type II collagen-induced arthritis was established in male DBA/1J mice at described Wooley and Geiger (Wooley, P.H., Methods in Enzymology, 162, pp. 361-373 (1988) and Geiger, T., Clinical and Experimental Rheumatology, 11, pp. 515-522 (1993)). Chick sternum Type II collagen (4 mg/kg in 10 mM acetic acid) was emulsified with an equal volume of Freund's complete adjuvant (FCA) by repeated passages (400) between two 10 ml glass syringes with a gauge 16 double-hub needle. Mice were immunized by intradermal injection (50 μl; 100μl CII per mouse) of collagen emulsion 21 days later at the contra-lateral side of the tail base. Drugs were administered twice a day (10, 25 and 50 mg/kg) by oral gavage approximately 7 h apart. Vehicles used included ethanol/PEG/water, β-cyclodextrin, labrosol/water or cremophor/water. Drug treatments were initiated within 2 h of the CII booster

immunization. Inflammation was scored on a 1 to 4 scale of increasing severity on the two front paws and the scores are added to give the final score.

Results in the **Figs. 12, 13** and **14** show prodrugs **412f, 412d** and **696a** inhibit inflammation in collagen-induced arthritits in mice after oral adminstration. Compound **214e** did not inhibit inflammation when dosed (50 mg/kg) once a day by oral gavage.

Example 22

In vivo bioavailability determination

The drugs (10-100 mg/kg) were dosed orally to rats (10 mL/kg) in ethanol/PEG/water, β-cyclodextrin, labrosol/water or cremophor/water. Blood samples were drawn from the carotid artery at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing, centrifuged to plasma and stored at -70°C until analysis. Aldehyde concentrations were determined using an enzymatic assay. Pharmacokinetic analysis of data was performed by non-linear regression using RStrip (MicroMath Software, UT). Drug availability values were determined as follows: (AUC of drug after oral prodrug dosing/AUC of drug after i.v. dosing of drug)x(dose i.v./dose p.o.) x100%.

Results in Table 21 show that prodrugs **412f, 412d** and **696a** give significant blood levels of drug and have good drug availability when dosed orally. Blood levels of **214e** were not detected when it was dosed orally.

Table 21 Oral Bioavailability of **412f, 412d, 696a and 214e** in Rat.

Compound	Dose (mg/kg)	Cmax (μg/ml)	Drug Availability (%)
412f	25	2.4	32
412d	25	2.6	35
696a	50	1.2	10
214e	45	0.2	0.9%

Example 23

ICE cleaves and activates pro-IGIF

ICE and ICE homolog expression plasmids

A 0.6 kb cDNA encoding full length murine pro-IGIF (H. Okamura et al., Nature, 378, p. 88 (1995) was ligated into the mammalian expression vector pCDLSRα (Y. Takebe et al., Mol. Cell Biol., 8, p. 466 (1988)).

Generally, plasmids (3 μg) encoding active ICE (above), or the three ICE-related enzymes TX, CPP32, and CMH-1 in the pCDLSRα expression vector (C. Faucheu et al., EMBO, 14, p. 1914 (1995); Y. Gu et al., EMBO, 14, p. 1923 (1995); J. A. Lippke et al., J. Biol. Chem., 271, p. 1825 (1996)), were transfected into subconfluent monolayers of Cos cells in 35-mm dishes using the DEAE-dextran method (Y. Gu et al., EMBO J., 14, p. 1923 (1995)). Twenty-four hours later, cells were lysed and the lysates subjected to SDS-PAGE and immunoblotting using an antiserum specific for IGIF (H. Okamura et al., Nature, 378, p. 88 (1995).

Polymerase chain reaction was used to introduce Nde I sites at the 5' and 3' ends of the murine pro-IGIF cDNA using the following primers: GGAATTCCATATGGCTGCCATGTCAGAAGAC (forward) and GGTTAACCATATGCTAACTTTGATGTAAGTTAGTGAG (reverse). The

resulting NdeI fragment was ligated into E. coli expression vector pET-15B(Novagen) at the NdeI site to create a plasmid that directs the synthesis of a polypeptide of 213 amino acids consisting of a 21-residue peptide (MGSSHHHHHHSSGLVPRGSHM, where LVPRGS represents a thrombin cleavage site) fused in-frame to the N-terminus of pro-IGIF at Ala2, as confirmed by DNA sequencing of the plasmid and by N-terminal sequencing of the expressed proteins. E. coli strain BL21(DE3) carrying the plasmid was induced with 0.8 mM isopropyl-1-thio-β-D-galactopyranoside for 1.5 hours at 37°C, harvested, and lysed by microfluidization (Microfluidic, Watertown, MA) in Buffer A (20 mM sodium phosphate, pH 7.0, 300 mM NaCl, 2 mM dithiothreitol, 10% glycerol, 1 mM phenylmethylsulfonyl fluoride, and 2.5 μg/ml leupeptin). Lysates were cleared by centrifugation at 100,000 x g for 30 min. (His)6-tagged pro-IGIF protein was then purified from the supernatant by Ni-NTA-agarose (Qiagen) chromatography under conditions recommended by the manufacturer.

In Vitro pro-IGIF Cleavage Reactions

In vitro cleavage reactions (30 μl) contained 2 μg of purified pro-IGIF and various concentrations of the purified proteases in a buffer containing 20 mM Hepes, pH 7.2, 0.1% Triton X-100, 2 mM DTT, 1 mM PMSF and 2.5 μg/ml leupeptin and were incubated for 1 hour at 37°C. Conditions for cleavage by granzyme B were as described previously (Y. Gu et al., J. Biol. Chem., 271, p. 10816 (1996)). Cleavage products were analyzed by SDS-PAGE on 16% gels and Coomassie Blue staining, and were subjected to N-terminal amino acid sequencing

using an ABI automated peptide sequencer under conditions recommended by the manufacturer.

Kinetic Parameters of IGIF Cleavage by ICE

The kinetic parameters (k_{cat}/K_M, K_M, and k_{cat}) for IGIF cleavage by ICE were determined as follows. ^{35}S-methionine-labeled pro-IGIF (3000 cpm, prepared by *in vitro* transcription and translation using, the TNT T7-coupled reticulocyte lysate system (Promega) and pro-IGIF cDNA in a pSP73 vector as template) were incubated in reaction mixtures of 60 µl containing 0.1 to 1 nM recombinant ICE and 190 nM to 12 µM of unlabeled pro-IGIF for 8-10 min at 37°C. Cleavage product concentrations were determined by SDS-PAGE and PhosphoImager analyses. The kinetic parameters were calculated by nonlinear regression fitting of the rate vs. concentration data to the Michaelis-Menten equation using the program Enzfitter (Biosoft).

IFN-γ Induction Assays

A.E7 Th1 cells (H. Quill and R. H. Schwartz, J. Immunol., 138, p. 3704 (1987)) (1.3×10^5 cells in 0.15 ml Click's medium supplemented with 10% FBS, 50 µM 2-mercaptoethanol and 50 units/ml IL-2) in 96-well plates were treated with IGIF for 18-20 hours and the culture supernatant were assayed for IFN-γ by ELISA (Endogen, Cambridge, MA).

Example 24

Processing of pro-IGIF by ICE in Cos Cells

Cos cells were transfected with various expression plasmid combinations as described in Example 23. Transfected Cos cells (3.5×10^5 cells in a 35-mm dish) were labeled for 7 hours with 1 ml of methionine-

free DMEM containing 2.5% normal DMEM, 1% dialyzed fetal bovine serum and 300 µCi/ml ^{35}S-methionine (^{35}S-Express Protein Labeling-Mix, New England Nuclear). Cell lysates (prepared in 20 mM Hepes, pH 7.2, 150 mM NaCl, 0.1% Triton X-100, 5 mM N-ethylmaleimide, 1 mM PMSF, 2.5 µg/ml leupeptine) or conditioned medium were immunoprecipitated with an antiIGIF antibody that recognizes both the precursor and the mature forms of IGIF (H. Okamura et al., Nature, 378, p. 88 (1995)). Immunoprecipitated proteins were analyzed by SDS-PAGE (polyacrylamide gel electrophoresis) and fluorography (**Fig. 2A**).

We also measured the presence of IFN-γ inducing activity in the cell lysates and the conditioned media of transfected cells (**Fig. 2B**). Transfected Cos cells (3.5×10^5 cells in a 35-mm dish) were grown in 1 ml medium for 18 hours. Media was harvested and used at 1:10 final dilution in the IFN-γ induction assay (Example 23). Cos cell pellets from the same transfection were lysed in 100 µl of 20 mM Hepes, pH 7.0, by freeze-thawing 3 times. Lysates were cleared by centrifugation as described above and were used at a 1:10 dilution in the assay.

Example 25

IGIF is a physiological substrate of ICE

Wild type (ICE+/+) and ICE-/- mice were primed with heat-inactivated *P. acnes*, and Kupffer cells were isolated from these mice 7 days after priming and were then challenged with 1 µg/ml LPS for 3 hours. The amounts of IGIF in the conditioned media were measured by ELISA.

Wild type or ICE-deficient mice were injected intraperitoneally with heat-killed p. acnes as described (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995)). Kupffer cells were prepared seven days later according to Tsutsui et al. (H. Tsutsui et al., Hepato-Gastroenterol., 39, p. 553 (1992)) except a nycodenz gradient was used instead of metrizamide. For each experiment, Kupffer cells from 2-3 animals were pooled and cultured in RPMI 1640 supplemented with 10% fetal calf serum and 1 μg/ml LPS. Cell lysates and conditioned medium were prepared 3 hours later.

Kupffer cells from wild type and ICE-/- mice were metabolically labeled with ^{35}S-methionine as for Cos cells (described above in Example 24) except that methionine-free RPMI 1640 was used in place of DMEM. IGIF immunoprecipitation experiments were performed on cell lysates and conditioned media and immunoprecipitates were analyzed by SDS-PAGE and fluorography as described in Example 23. See **Fig. 3.**

Example 26

Induction of IFN-γ Production In Vivo

LPS mixed with 0.5% carboxymethyl cellulose in PBS, pH 7.4, was administered to mice by intraperitoneal injection (30 mg/kg LPS) in a dose volume of 10 ml/kg. Blood was collected every 3 h for 24 h from groups of three ICE-deficient or wild type mice. Serum IFN-γ levels were determined by ELISA (Endogen).

Example 27

IGIF and IFN-γ Inhibition Assays

Inhibition of IGIF processing by ICE inhibitors was measured in ICE inhibition assays as described herein (see Example 1 and Table 22).

Human PBMC Assays

Human buffy coat cells were obtained from blood donors and peripheral blood mononuclear cells (PBMC) were isolated by centrifugation in LeukoPrep tubes (Becton-Dickinson, Lincoln Park, NJ). PBMC were added (3×10^6/well) to 24 well Corning tissue culture plates and after 1 hr incubation at 37°C, non-adherent cells were removed by gently washing. Adherent mononuclear cells were stimulated with LPS (1 µg/ml) with or without ICE inhibitor in 2 ml RPMI-1640-10% FBS. After 16-18 hr incubation at 37°C, IGIF and IFN-γ were quantitated in culture supernatants by ELISA.

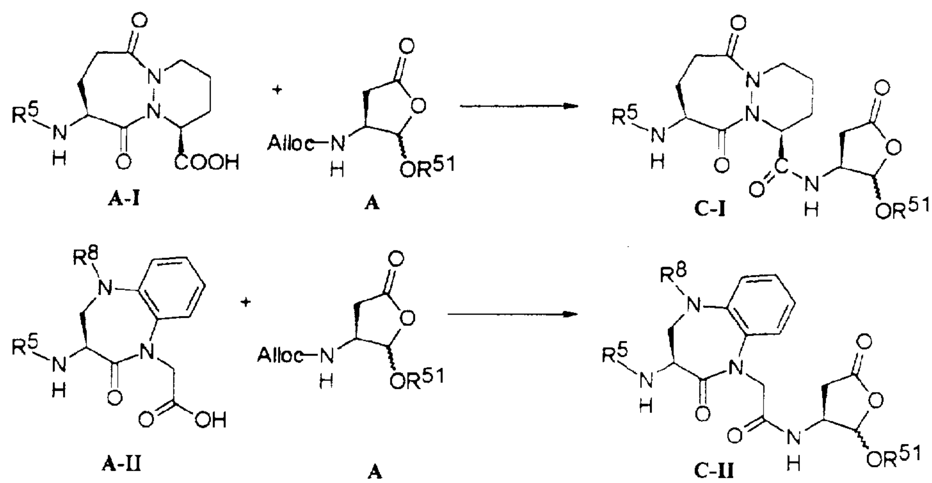
For example, we obtained the following data for compound **412** of this invention using the methods described herein. The structure of compound **412** is shown below.

Table 22

compound	UV-Visible K_i (nM)	Cell PBMC avg. IC50 (nM)
412	1.3	580

Example 28

Compounds of this invention may be prepared via various methods. The following illustrates a preferred method:

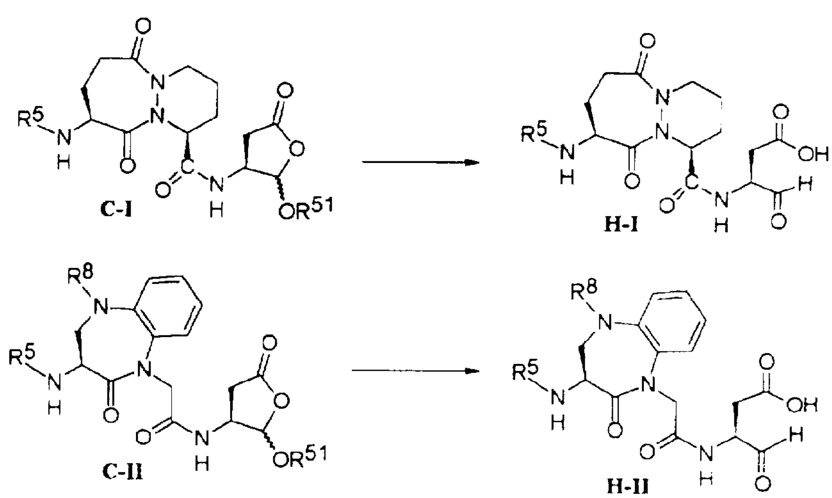


To a solution of **A** (1.1 equivalent) in CH_2Cl_2 (or DMF, or CH_2Cl_2:DMF (1:1)) is added triphenylphosphine (0-0.5 equivalent), a nucleophilic scavenger (2-50 equivalents) and tetrakis-triphenylphosphine palladium(0) (0.05-0.1 equivalent) at ambient temperature under inert atmosphere (nitrogen or argon). After 10 minutes, the above reaction mixture is optionally concentrated, then a solution of acid **A-I** or **A-II** in CH_2Cl_2 (or DMF, or CH_2Cl_2:DMF (1:1)) is added followed by addition of HOBT (1.1 equivalent) and EDC (1.1 equivalent). The resulting reaction mixture is allowed to stir at ambient temperature 1 hour-48 hours to provide coupled products **C-I** or **C-II**.

Various nucleophilic scavengers may be used in the above process. Merzouk and Guibe, Tetrahedron Letters, 33, pp. 477-480 (1992); Guibe and Balavoine, Journal of Organic Chemistry, 52, pp. 4984-4993

(1987)). Preferred nucleophilic scavengers that may be used include: dimedone, morpholine, trimethylsilyl dimethylamine and dimethyl barbituric acid. More preferred nuclophilic scavengers are trimethylsilyl dimethylamine (2-5 equivalents) and dimethyl barbituric (5-50 equivalents). When the nucleophilic scavenger is trimethylsilyl dimethylamine, the above reaction mixture must be concentrated prior to addition of **A-I** or **A-II**.

Other compounds of this invention may be prepared by hydrolyzing compounds represented by **C-I** and **C-II** to compounds represented by **H-I** and **H-II** as described in the following scheme:

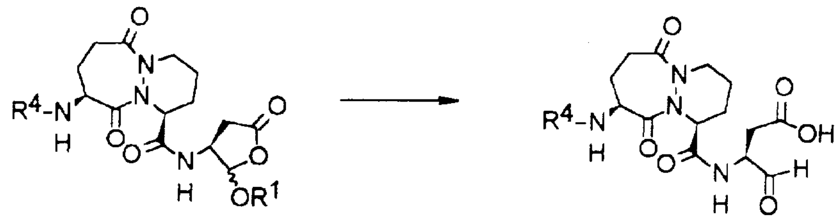


The hydrolysis may be carried out under various conditions, provided that the conditions include an acid and H_2O. Acids that may be used include p-toluensulfonic, methanesulfonic acid, sulfuric, perchloric, trifluoroacetic, and hydrochloric. For example, trifluoroacetic acid (1-90% by weight) or

hydrochloric acid (0.1-30% by weight) in CH_3CN/H_2O (1-90% H_2O by weight) at between 0-50 °C may be used.

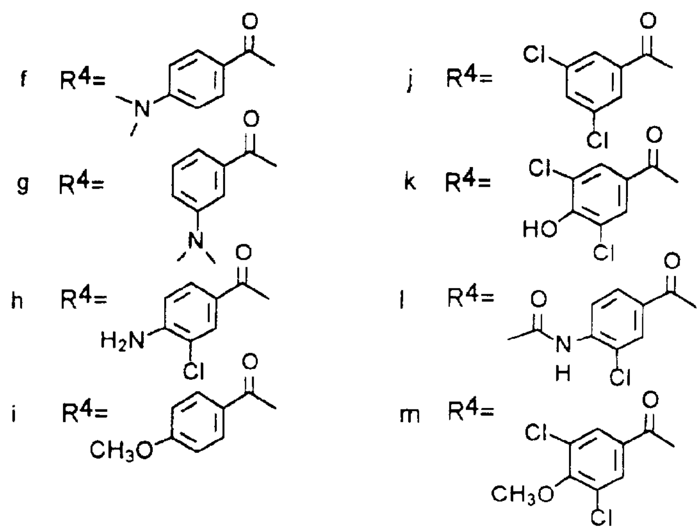
Example 29

Compounds **213f**, **213g**, **213h**, **213i**, **213j**, **213k**, **213l**, **213m**, **214f**, **214g**, **214h**, **214i**, **214j**, **214k**, **214l**, **214m**, **550f**, **550g**, **550h**, **550i**, **550j**, **550k**, **550l** and **550m** were prepared as follows.



213f-m, R^1 = Bn
550f-m, R^1 = Et

214f-m



[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213f), was synthesized from **212f** by the methods used to

prepare **213e** from **212e** to afford 504 mg of **213f** as a yellow solid, ^{1}H NMR (CD_3OD) δ 1.10(br. m, 0.25H), 1.30(br. m, 2H), 1.50(br. m, 1H), 1.65(br. m, 1.5H), 1.80(br. m, 0.25H), 1.90(br. m, 0.25H), 1.95(br. m, 0.5H), 2.05(br. m, 0.25H), 2.15(m, 1H), 2.3(m, 1H), 2.5(br. m, 1H), 2.6(dd, 1H), 2.8(m, 1H), 3.1(br. s, 3H), 3.15(br. m, 1H), 3.32(br. s, 3H), 3.5(m, 1H), 4.5(br. m, 1H), 4.62(d, 0.25H), 4.72(m, 3H), 4.95(m, 1H), 5.1(br. t, 0.25H), 5.15(br. t, 0.75H), 5.7(d, 1H), 6.75(d, 2H), 7.35(br. s, 5H), 7.75(d, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213g), was synthesized from **212g** by the methods used to prepare **213e** from **212e** to afford 400 mg of **213g**, ^{1}H NMR (CD_3OD) δ 1.5(br. m, 1H), 1.65(br. m, 2H), 1.70(br. m, 0.25H), 1.90(br. m, 1H), 1.95(br. m, 1H), 2.05(br. m, 0.25H), 2.10(m, 1H), 2.3(m, 1H), 2.5(m, 2H), 2.59(d, 1H), 2.6(d, 1H), 2.78(d, 1H), 2.8(d, 1H), 2.93(br. s, 4H), 3.05(br. m, 1H), 3.15(br. m, 0.25H), 3.3(br. s, 3H), 3.5(m, 2H), 4.5(br. m, 2H), 4.65(d, 1H), 4.7(br. m, 2H), 4.95(br. m, 1H), 5.15(br. t, 0.25H), 5.2(br. t, 0.75H), 5.2(d, 1H), 6.95(d, 1H), 7.15(d, 1H), 7.25(br. s, 1H), 7.3(br. t, 2H), 7.45(br. s, 6H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-aminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213h), was synthesized from **212h** by the methods used to

prepare **213e** from **212e** to afford 296 mg of **213h**, ^{1}H NMR ($CDCl_3$) δ 1.55-1.68(m, 1H), 1.7-2.05(m, 3H), 2.3-2.5(m, 2H), 2.65-2.8(m, 1H), 2.85-2.93(m, 1H), 2.95-3.25(m, 3H), 4.44-4.65(m, 2H), 4.68-4.82(m, 1H), 4.9-4.95(d, 1H), 5.05-5.18(m, 2H), 5.28(s, 0.5H), 5.55-5.58(d, 0.5H), 6.52-6.58(d, 0.5H), 6.7-6.76(m, 2H), 6.82-6.85(d, 0.5H), 7.3-7.4(m, 5H), 7.52-7.58(m, 1H), 7.75(s, 0.5H), 7.8(s, 0.5H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213i), was synthesized from **212i** by the methods used to prepare **213e** from **212e** to afford 1.1 g of **213i**, ^{1}H NMR ($CDCl_3$) δ 1.55-2.05(m, 6H), 2.26-2.5(m, 2H), 2.68-2.82(m, 1H), 2.85-2.92(m, 1H), 2.95-3.25(m, 2H), 3.82(s, 1.5H), 3.85(s, 1.5H), 4.4-4.65(m, 2H), 4.7-4.78(m, 1H), 4.88-4.95(m, 1H), 5.05-5.23(m, 1H), 5.28(s, 0.5H), 5.55-5.58(d, 0.5H), 6.6-6.65(m, 1H), 6.8-6.84(m, 1H), 6.9-6.95(m, 3H), 7.3-7.45(m, 4H), 7.78-7.85(m, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichlorobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213j), was synthesized from **212j** by the methods used to prepare **213e** from **212e** to afford 367 mg of **213j**, ^{1}H NMR ($CDCl_3$) δ 1.55-2.05(m, 12H), 2.25(d, 1H), 2.35(m, 1H), 2.48(m, 2H), 2.75(m, 2H), 2.9(m, 1H), 2.95-3.25(m, 5H), 4.45(t, 1H), 4.5-4.6(m, 4H), 4.7(m, 1H), 4.75(d, 1H),

4.88(m, 1H), 5.05(m, 2H), 5.15(q, 1H), 5.3(s, 1H), 5.58(d, 1H), 6.5(d, 1H), 6.9(d, 1H), 7.05(d, 1H), 7.25-7.35(m, 5H), 7.6(s, 2H), 7.7(s, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-hydroxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213k), was synthesized from **212k** by the methods used to prepare **213e** from **212e** to afford 593 mg of **213k**, ^{1}H NMR (CD_3OD) δ 1.5(m, 1H), 1.6-1.7(m, 2H), 1.75-1.95(m,4H), 2.15(m, 2H), 2.3(m, 1H), 2.6(m, 1H), 2.7(m, 1H), 3.05(m, 2H), 3.15(m, 1H), 3.5(m, 2H), 4.45(m, 2H), 4.65(d, 1H), 4.7(m, 1H), 4.95(m, 1H), 5.15(m, 1H), 5.4(s, 1H), 5.7(d, 1H), 7.3(m, 5H), 7.85(s, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-acetamidobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213l), was synthesized from **212l** by the methods used to prepare **213e** from **212e** to afford 133 mg of **213l**, ^{1}H NMR ($CDCl_3$) δ 1.55-1.7(m, 1H), 1.75-2.05(m, 3H), 2.25(s, 1.5H), 2.27(s, 1.5H), 2.3-2.48(m, 2H), 2.7-2.83(m, 1H), 2.85-2.94(dd, 1H), 2.95-3.25(m, 2H), 4.42-4.65(m, 2H), 4.68-4.85(m, 1H), 4.88-4.95(m, 1H), 5.05-5.18(m, 2H), 5.32(s, 0.5H), 5.55-5.6(d, 0.5H), 6.48-6.55(d, 1H), 6.88-6.92(d, 1H), 7.0-7.04(d, 0.5H), 7.15-7.2(d, 0.5H), 7.3-7.4(m, 4H), 7.64-7.78(m, 2H), 7.88-7.94(m, 1H), 8.45-8.56(m, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-

octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213m), was synthesized from **212m** by the methods used to prepare **213e** from **212e** to afford 991 mg of **213m**, ^{1}H NMR ($CDCl_3$) δ 1.5-2.15(m, 5H), 2.2-2.55(m, 3H), 2.6-3.3(m, 4H), 3.95(2s, 3H), 4.45-4.7(m, 2H), 4.7-4.85(m, 1H), 4.8504.95(m, 1H), 5.05-5.25(m, 1H), 5.3(s, 0.5H), 5.6(d, 0.5H), 6.55(d, 0.5H), 6.85(d, 0.5H), 7.0(d, 0.5H), 7.25-7.6(m, 5.5H), 7.75(s, 1H), 7.85(s, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550f), was synthesized from **212f** by the methods used to prepare **213e** from **212e** to afford 420 mg of **550f** as an off white solid, ^{1}H NMR ($CDCl_3$) δ 1.2-1.25(br. t, 3H), 1.35(m, 1H), 1.55(br. m, 1H), 1.88-2.02(br. m, 4H), 2.3(d, 1H), 2.35(m, 1H), 2.45(m, 1H), 2.55-2.75(m, 3H), 3.0(s, 6H), 3.25(m, 1H), 3.55(m, 1H), 3.65(m, 1H), 3.75(m, 1H), 3.9(m, 1H), 4.3(t, 1H), 4.55(m, 2H), 4.68(br. m, 1H), 3.9(m, 1H), 4.3(t, 1H), 4.55(m, 2H), 4.68(br. m, 1H), 4.95(br. m, 1H), 5.1(br. m, 2H), 5.45(d, 1H), 6.5(m, 2H), 7.7(m, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-aminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550h), was synthesized from **212h** by the methods used to prepare **213e** from **212e** to afford 195 mg of **550h** as a white solid, ^{1}H NMR (DMSO-d_6) δ 1.1-1.18(2t, 3H), 1.6-

1.7(m, 2H), 1.88-2.05(m, 2H), 2.1-2.35(m, 3H), 2.48-2.56(m, 1H), 2.75-2.8(m, 0.75H), 2.88-3.08(m, 1.25H), 3.25-3.4(m, 1H), 3.55-3.8(m, 2H), 4.35-4.45(m, 1H), 4.55-4.62(m, 1H), 4.8-4.88(m, 1H), 4.98-5.03(m, 0.25H), 5.1-5.13(m, 0.75H), 5.33(s, 0.25H), 5.58-5.6(d, 0.75H), 5.9-6.0(br. s, 2H), 6.8-6.85(d, 1H), 7.58-7.62(d, 1H), 7.82(s, 1H), 8.22-8.28(d, 1H), 8.48-8.52(d, 0.75H), 8.72-8.76(d, 0.25H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550i), was synthesized from **212i** by the methods used to prepare **213e** from **212e** to afford 135 mg of **550i**, ^{1}H NMR ($CDCl_3$) δ 1.18-1.28(2t, 3H), 1.6-1.75(m, 1.5H), 1.9-2.1(m, 3.5H), 2.22-2.3(d, 0.5H), 2.38-2.47(m, 1.5H), 2.7-2.8(m, 0.5H), 2.8-2.93(m, 1H), 2.94-3.15(m, 1.5H), 3.15-3.28(m, 1H), 3.55-3.62(q, 0.5H), 3.62-3.73(q, 0.5H), 3.78-3.88(q, 0.5H), 3.88(s, 3H), 3.9-3.95(q, 0.5H), 4.33-4.4(m, 0.5H), 4.5-4.55(m, 1H), 4.68-4.76(m, 0.5H), 4.9-4.95(m, 0.5H), 5.1-5.2(m, 1.5H), 5.18(s, 0.5H), 5.48-5.52(d, 0.5H), 6.48-6.55(d, 0.5H), 6.85-6.9(m, 1H), 6.9-6.95(m, 2H), 7.34-7.38(d, 0.5H), 7.78-7.85(m, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-hydroxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550k), was synthesized from **212k** by the methods used to prepare **213e** from **212e** to afford 174 mg of **550k** as a white solid, ^{1}H NMR (DMSO-d_6) δ 1.15(2t, 3H), 1.6-

1.75(m, 2H), 1.9-2.05(m, 2H), 2.1-2.4(m, 5H), 2.5-2.55(m, 1H), 2.7-2.8(m, 0.5H), 2.85-3.0(m, 1H), 3.0-3.1(m, 0.5H), 3.55-3.7(m, 1H), 3.7-3.8(m, 1H), 4.2(t, 0.5H), 4.35-4.45(m, 0.5H), 4.55-4.65(m, 0.5H), 4.8-4.9(m, 0.5H), 5.05(t, 0.5H), 5.15(t, 0.5H), 5.35(s, 0.5H), 5.6(d, 0.5H), 7.95(s, 2H), 8.5(d, 0.5H), 8.65(d, 1H), 8.75(d, 0.5H), 10.9(br. s, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-acetamidobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550l), was synthesized from **212l** by the methods used to prepare **213e** from **212e** to afford 151 mg of **550l**, ^{1}H NMR ($CDCl_3$) δ 1.2-1.28(2t, 3H), 1.6-1.72(m, 1.5H), 1.88-2.15(m, 3.5H), 2.22-2.28(m, 0.5H), 2.28(s, 3H), 2.38-2.48(m, 1.5H), 2.66-2.92(m, 1.5H), 2.95-3.14(m, 1.5H), 3.2-3.34(m, 1H), 3.56-3.63(q, 0.5H), 3.63-3.72(q, 0.5H), 3.8-3.85(q, 0.5H), 3.9-3.95(q, 0.5H), 4.32-4.38(m, 0.5H), 4.5-4.62(m, 1H), 4.68-4.75(m, 0.5H), 4.88-4.92(m, 0.5H), 5.08-5.2(m, 1.5H), 5.18(s, 0.5H), 5.46-5.5(d, 0.5H), 6.5-6.55(d, 0.5H), 6.98-7.05(m, 1H), 7.42-7.48(d, 0.5H), 7.63-7.78(m, 2.5H), 7.9-7.94(d, 0.5H), 8.44-8.52(m, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550m), was synthesized from **212m** by the methods used to prepare **213e** from **212e** to afford 301 mg of **550m** as a white solid, ^{1}H NMR ($CDCl_3$) δ 1.2-1.35(2t, 3H), 1.5-

1.8(m, 2H), 1.9-2.15(5H), 2.25(d, 0.5H), 2.4-2.5(m, 2H), 2.65-2.8(m, 0.5H), 2..8-3.0(m, 0.5H), 3.0-3.2(m, 1H), 3.2-3.35(m, 0.5H), 3.55-3.65(m, 0.5H), 3.65-3.75(m, 0.5H), 3.8-3.9(m, 0.5H), 3.9-4.0(m, 0.5H), 4.4-4.45(m, 0.5H), 4.55-4.65(m, 0.5H), 4.7-4.8(m, 0.5H), 4.85-4.95(m, 0.5H), 5.05-5.2(m, 0.5H), 5.2(s, 0.5H), 5.5(d, 0.5H), 6.5(d, 0.5H), 6.9(d, 0.5H), 6.95(d, 0.5H), 7.35(d, 0.5H), 7.75(s, 1H), 7.85(s, 1H).

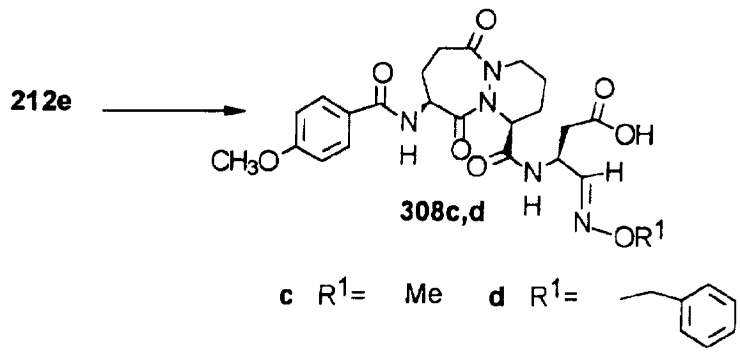
[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichlorobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214j), was synthesized from **213j** by the method used to prepare **2002** from **2001** to afford 62 mg of **214j** as a white solid, ^{1}H NMR (CD_3OD) δ 0.9 (t, 1H), 1.3(br. s, 1H), 1.7(br. m, 1H), 1.9(br. m, 1H), 2.1(br. s, 1H), 2.25(q, 1H), 2.35(m, 1H), 2.48(m, 2H), 2.65(t, 1H), 3.15(br. t, 1H), 3.5(br. m, 1H), 4.3(br. s, 1H), 4.55(m, 2H), 4.95(t, 1H), 5.25(br. s, 1H), 7.6(br. s, 1H), 7.85(br. s, 1H).

[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichloro-4-hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214k), was synthesized from **213k** by the method used to prepare **2002** from **2001** to afford 80 mg of **214k** as a white solid, ^{1}H NMR (CD_3OD) δ 1.6-1.7(m, 1H), 1.8-2.0(m, 2H), 2.0-2.1(m, 2H), 2.15-2.25(m, 1H), 2.3-2.4(m, 1H), 2.4-2.55(m, 2H), 2.6-2.75(m,1H), 3.05-3.2(m, 1H), 3.4-3.6(m, 2H), 4.2-4.3(m, 1H), 4.45-4.6(m, 1H), 4.8-5.0(m, 1H), 5.1-5.2(m, 1H), 7.85(s, 2H).

[3S(1*S*,9*S*)]3-(9-(3-Chloro-4-acetamidobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (2141), was synthesized from **2131** by the method used to prepare **2002** from **2001** to afford 91 mg of **2141** as a white solid, ^{1}H NMR (DMSO-d_6) δ 1.65(br. m, 6H), 1.9(br. m, 6H), 2.15(s, 3H), 2.3(m, 3H), 2.6-2.85(m, 3H), 2.9(m, 2H), 3.0(m, 1H), 4.15(br. q, 1H), 4.4(m, 3H), 5.0(m, 1H), 5.15(m, 1H), 5.45(s, 1H), 7.8(d, 2H), 7.95(d, 1H), 8.05(s, 1H), 8.65(m, 2H), 9.65(s, 1H).

[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichlorobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214m), was synthesized from **213m** by the method used to prepare **2002** from **2001** to afford 105 mg of **214m** as a white solid, ^{1}H NMR (CD_3OD) δ 1.6-1.75(m, 1H), 1.85-1.95(m, 1H), 2.0-2.1(m, 2H), 2.15-2.25(m, 1H), 2.3-2.4(m, 1H), 2.45-2.55(m, 2H), 2.65-2.75(m, 1H), 3.4-3.55(m, 2H), 3.95(s, 3H), 4.2-4.3(m, 1H), 4.45-4.6(m, 1H), 4.9-5.0(m, 1H), 5.15-5.2(m, 1H), 7.9(s, 2H).

Compounds **308c** and **308d** were prepared as follows.

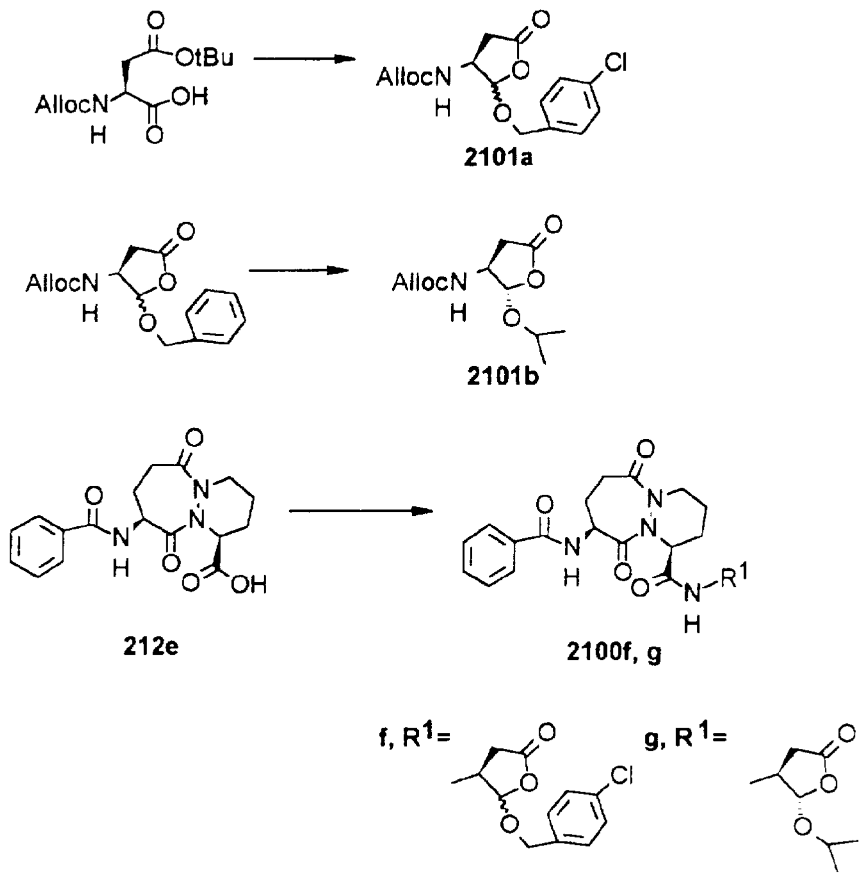


[3*S*(1*S*,9*S*) 3-(9-(4-Methoxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-amino]-4-oxobutanoic acid, O-methyl oxime (308c), was synthesized from **212e** via the methods used to prepare **308b** from **212e** to afford 266 mg of **308c** ^{1}H NMR ($CDCl_3$) δ 1.6-1.7(m, 1H), 1.88-1.98(m, 3H), 2.02-2.15(m, 1H), 2.3-2.4(m, 1H), 2.65-2.95(m, 3H), 3.04-3.09(m, 1H), 3.12-3.25(m, 1H), 3.84(s, 3H), 3.86(s, 3H), 4.5-4.58(m, 1H), 4.88-4.95(m, 1H), 5.1-5.25(m, 2H), 6.86-6.9(d, 2H), 7.15-7.25(m, 2H), 7.36-7.4(m, 1H), 7.75-7.8(d, 2H).

[3*S*(1*S*,9*S*) 3-(9-(4-Methoxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-amino]-4-oxobutanoic acid, O-benzyl oxime (308d), was synthesized from **212e** via the methods used to prepare **308b** from **212e** to afford 270 mg of **308d**, ^{1}H NMR ($CDCl_3$) δ 1.55-1.65(m, 1H), 1.8-2.1(m, 4H), 2.3-2.4(m, 1H), 2.65-2.88(m, 3H), 2.9-3.3(m, 3H), 4.5-4.58(m, 1H), 4.88-4.95(m, 1H), 5.05(s, 2H), 5.1-5.2(m, 1H), 6.82-

6.95(m, 2H), 7.02-7.15(m, 2H), 7.28(m, 5H), 7.45(m, 1H), 7.72(d, 2H).

Compounds **2100f, 2100g, 2100h, 2100i** and **2100j** were prepared as described below.



(3*S*,2*RS*) 3-Allyloxycarbonylamino-2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran (2101a), was synthesized from allyloxycarbonylamino-β-*tert*-butyl aspartate by the methods employed by Chapman (<u>Bioorg. & Med. Chem. Lett.</u>, 2, pp.615-618 (1992)) to prepare (3*S*,2*RS*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran

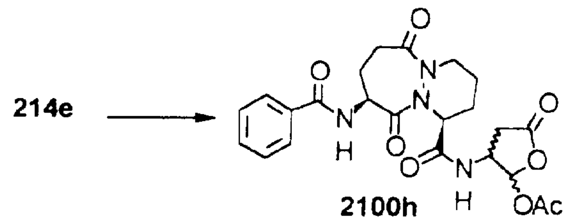
using 4-chlorobenzyl alcohol instead of benzyl alcohol to afford 1.84 g of **2101a** as a crystalline solid.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100f), was synthesized from **212e** by the methods used to prepare **213e** from **212e** using **2101a** to afford 380 mg of **2100f**, ^{1}H NMR ($CDCl_3$) δ 1.8-2.0(m, 10H), 2.30(d, 1H), 2.31-2.5(m, 3H), 2.7-2.9(m, 3H), 3.05(m, 2H), 3.1-3.2(m, 4H), 4.45(q, 1H), 4.5-4.6(m, 3H), 4.7(d, 2H), 4.85(d, 1H), 4.9(t, 1H), 5.2(t, 1H), 5.15(m, 2H), 5.25(s, 1H), 5.55(d, 1H), 6.5(d, 1H), 6.9(d, 1H), 6.95(d, 1H), 7.25(m, 3H), 7.35(t, 2H), 7.45(m, 2H), 7.55(1H), 7.8(m, 3H).

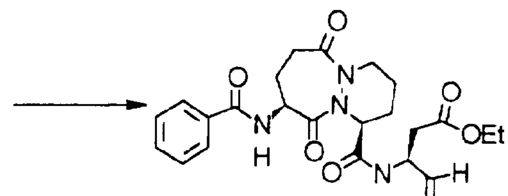
(3*S*,2*RS*) 3-Allyloxycarbonylamino-2-*anti*-isopropoxy-5-oxotetrahydrofuran (2101b), was synthesized from (3*S*,2*RS*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran via the method used to prepare **2100d** from **214e** using H_2SO_4 instead of pTSA to afford **2101b**.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-*anti*-isopropoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100g), was synthesized from **212e** by the methods used to prepare **213e** from **212e** using **2101b** to afford 31 mg of **2100g**, ^{1}H NMR ($CDCl_3$) δ 1.19 (d), 1.94 (br s), 2.00-2.12 (m), 2.24 (d), 2,42 (dd), 2.71-2.83 (m), 3.02 (dd), 3.12-3.27 (overlapping m), 3.93 (m), 4.32-4.37 (m,),

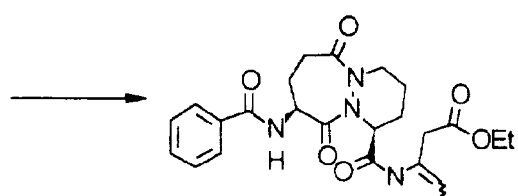
4.52-4.63 (m), 4.90-4.95 (m), 5.12-5.20 (m), 5.28 (s), 6.93 (d), 7.10 (d), 7.41-7.50 (m), 7.51-7.58 (m), 7,84 (d).



[1*S*,9*S*(2*RS*,3*RS*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-acetoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100h). A solution of **214e** (287 mg, 0.65 mmol) in pyridine (5 mL) was treated with Ac_2O (0.4 mL, 3.62 mmol). After 6 hours, the reaction mixture was poured into 5% $NaHSO_4$ and extracted 3 times with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (SiO_2, EtOAc) afforded 119 mg of **2100h**, ^{1}HNMR ($CDCl_3$, mixture of four diastereoisomers) δ 1.80-2.05(m), 2.12(s), 2.13(s), 2.19(s), 2.22(d), 2.67-2.75(m), 2.80-2.95(m), 3.00-3.20(m), 3.21-3.33(m), 3.50-3.95(four discrete multiplets), 4.19(m), 4.55(m), 4.57-4.65(m), 4.69(m), 4.85-4.95(m), 5.04(m), 5.10(s), 5.10-5.22(m), 6.46(d), 6.03(s), 6.50(d), 6.58(d), 6.75(d), 6.95-7.05(m), 7.22(m), 7.30(m), 7.71(d), 7.75-7.83(m).

2100b

2100i

[3*S*(1*S*,9*S*)]3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid ethyl ester (2100i). To a solution of **2100b** (1.5 g, 2.7 mmol) in CH_3CN (10 mL) was added 1N HCl at ambient temperature. After 6 hours solid $NaHCO_3$ was added and the product extracted with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography (SiO_2, 30-100% CH_2Cl_2 in EtOAc) afforded 123 mg of **2100i**, ^1H NMR ($CDCl_3$) δ 1.25(t, 3H), 1.6-1.8(m, 1H), 1.9-2.2(m, 5H), 2.4-2.5(m, 1H), 2.75-2.9(m, 2H), 3.0-3.1(m, 2H), 3.2-3.25(m, 1H), 4.05-4.2(m, 1H), 4.5-4.7(m, 1H), 5.1-5.25(m, 1H), 7.0-7.2(m, 2H), 7.4-7.45(m, 2H), 7.5(t, 1H), 7.8(t, 2H), 9.5(s, 1H).

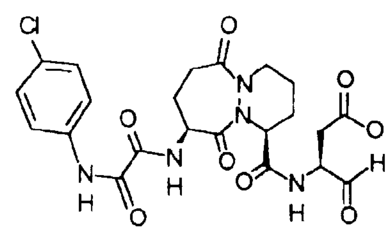
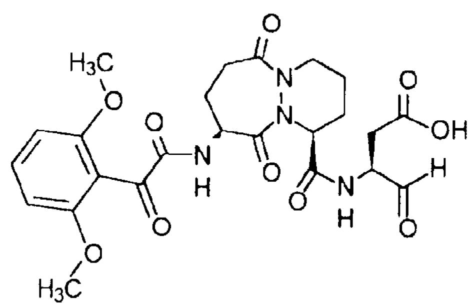
2100i

2100j

[3*S*(1*S*,9*S*)]3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-acetoxy-3-butenoic acid ethyl ester (2100j), was synthesized from **2100i** via the method used to prepare

2100h from **214e** to afford 347 mg of **2100j**, ^{1}H NMR ($CDCl_3$) δ 1.3(t, 3H), 1.6-1.8(m, 2H), 1.9-2.25(m, 4H), 2.25(s, 3H), 2.3-2.45(m, 1H), 2.8-3.0(m, 1H), 3.0-3.25(m, 2H), 3.4-3.45(m, 2H), 4.1-4.2(m, 2H), 4.55-4.7(m, 1H), 5.1-5.25(m, 1H), 6.8(s, 1H), 7.0-7.1(m, 2H), 7.5(t, 1H), 7.8(t, 2H), 9.5(s, 1H).

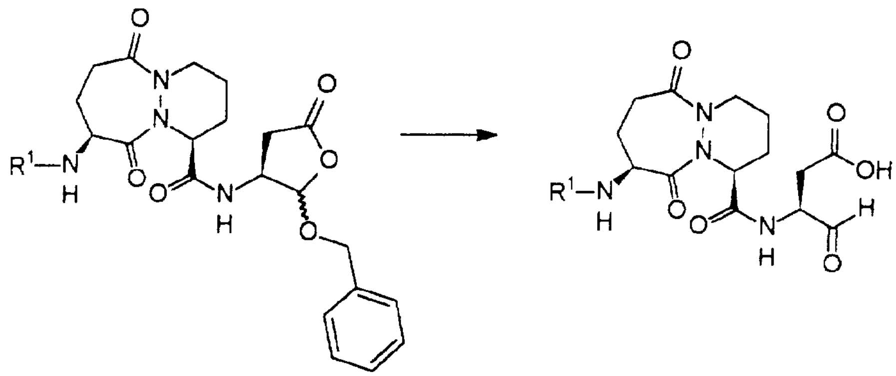
Compounds **500** and **501** are described in Table 23. These compounds were prepared by methods similar to the methods used to prepare compounds **404-449** (see, Example 11).

Table 23

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+H)+
500		C22H24ClN5O8	521.92	11.448 (A) 0.991	523.1
501		C24H28N4O10	532.51	10.13 0.97	533

The compounds described below (**213m**, **213n**, **213o**, **213p**, **213q**, **213r**, **213s**, **213t**, **213u**, **213v**, **213w**, **213x**, and **214w**), were prepared by methods similar to the methods used to prepare compounds **213b-f**.

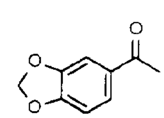
Compounds **419**, **415**, **450**, **456**, **475**, **404**, **486**, **487**, **417**, **408** and **418** may also be prepared as described below.

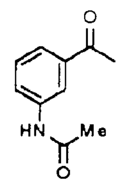
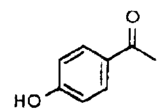
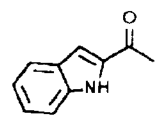
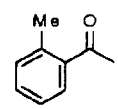
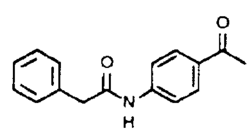
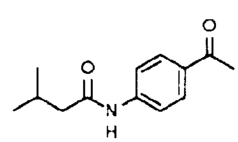
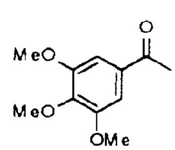


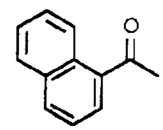
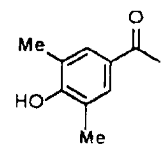
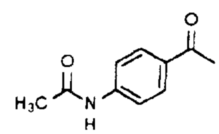
213m-x
214w, **404**, **408**, **415**,

417, **418**, **419**, **450**,

456, **475**, **486**, **487**

compound	R^1
213m, **419**	MeOC(O)-
213n, **415**	

213o, 450	
213p, 456	
213q, 475	
213r, 404	
213s, 486	
213t, 487	
213u, 417	

213v, 408	
213w, 214w	
213x, 418	

[1*S*,9S(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213n), was isolated as a mixture of diastereomers (syn:anti isomer ratio 6:4) (1.43g, 82%) as a white solid: mp. 206-10°C; IR (KBr) 3288, 1787, 1680, 1657, 1651, 1619, 1548, 1440, 1256, 1135; ^{1}H NMR (D_6-DMSO) δ 8.75 (0.4H, d), 8.55 (0.6H, d), 8.45 and 8.43 (1H, 2 x d), 7.50 (1H, d), 7.42 (1H, s), 7.40-7.27 (5H, m), 7.01 (1H, d), 6.11 (2H, s), 5.67 (0.6H, d), 5.43 (0.4H, s), 5.10-5.00 (1H, m), 4.90-4.59 (3.5H, m), 4.45-4.25 (1.5H, m), 3.47-3.20 (1H, m), 3.20-2.70 (2H, m), 2.65-2.35 (1H, m), 2.35-2.00 (3H, m), 2.00-1.75 (2H, m), 1.65-1.40 (2H, m). Anal. Calcd for $C_{29}H_{30}N_4O_9$: C, 60.20; H, 5.23; N, 9.68. Found: C, 60.08; H, 5.32; N, 9.50. MS (ES^+)

580 (M^+ + 2, 35%), 579 (M^+ + 1, 100), 404 (5), 367 (5), 236 (7), 107 (5).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Acetamido)benzamido]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213o), anti-isomer as a white foamy solid (0.73g, 69%): mp. 135-40°C; $[\alpha]_D^{21}$ -37.3° (c 0.1, CH_2Cl_2); IR (KBr) 3452, 3310, 1790, 1664, 1659, 1650, 1549, 1425, 1258, 1121; ^{1}H NMR (D_6-DMSO) δ 10.11 (1H, s), 8.77 (1H, d), 8.57 (1H, d), 8.01 (1H, s), 7.76 (1H, d), 7.55 (1H, d), 7.45-7.25 (6H, m), 5.43 (1H, s), 5.08-5.00 (1H, m), 4.95-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.40-3.20 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.45-2.06 (4H, m), 2.06 (3H, s), 2.00-1.75 (2H, m), 1.70-1.40 (2H, m). Anal. Calcd for $C_{30}H_{33}N_5O_8 \cdot 0.75H_2O$: C, 59.54; H, 5.75; N, 11.57. Found: C, 59.40; H, 5.62; N, 11.50. MS (ES^+) 593 (M^+ + 2, 33%), 592 (M^+ + 1, 100), 574 (7), 487 (7), 475 (6), 385 (9), 373 (26), 318 (14), 296 (11), 266 (10), 221 (22).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(4-hydroxybenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213p), was isolated as a foam (1.2g, 77%): $[\alpha]_D^{20}$ -115° (c 0.20, CH_2Cl_2); IR (KBr) 3368, 2946, 1794, 1654, 1609, 1540, 1505, 1421, 1277, 1175, 1119, 980; ^{1}H NMR (D_6-DMSO) δ 10.1 (1H, s), 8.80 (0.5H, d, J = 6.6), 8.60 (0.5H, d, J = 7.2), 8.40-8.36 (1H, 2d), 7.82 (2H, d, J = 8.0), 7.41 (5H, bs), 6.86 (2H, d, J 8.6), 5.72 (0.5H,

d, J = 5.0), 5.49 (0.5H, bs), 5.13-5.07 (1H, m), 4.95-4.65 (2.5H, m), 4.49-4.38 (2.5H, m), 3.49-3.30 (2H, m), 3.21, 2.79 (2H, m), 2.40-1.41 (7H, m). MS (ES^+) 551.

[1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(indol-2-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213q), was isolated as a white glassy solid (80%): mp. 145-149°C; $[\alpha]_D^{23}$ -56.0° (c 0.05, CH_2Cl_2); IR (KBr) 3399-3319, 1791, 1657, 1543, 1420, 1253, 1119; ^1H NMR ($CDCl_3$) δ 9.54 (1H, s), 7.65 (1H, d, J = 7.9), 7.51 (1H, d, J = 6.9), 7.44-7.25 (7H, m), 7.18-7.06 (3H, m), 5.30-5.20 (1H, m), 5.27 (1H, s), 4.84 (1H, m), 4.79 (1H, d, J = 11.4), 4.56 (1H, d, J = 11.3), 4.47 (2H, m), 3.28 (1H, m), 3.10-2.97 (2H, m), 2.71 (1H, m), 2.47-2.37 (1H, m), 2.26 (1H, d, J = 17.9), 2.09 (1H, m), 1.83, 1.70, 1.51 (4H, 3m).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(2-toluoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213r), was isolated as a mixture of diastereomers (syn:anti isomer ratio 55:45) as a white foamy solid (1.46g, 89%): mp. 106-10°C; IR (KBr) 3306, 2947, 1791, 1659, 1650, 1535, 1421, 1256, 1122; ^1H NMR (D_6-DMSO) δ 8.76 (0.45H, d), 8.56 (0.55H, d), 8.49 and 8.47 (1H, 2 x d), 7.41-7.19 (9H, m), 5.67 (0.55H, d), 5.43 (0.45H, s), 5.11-5.02 (1H, m), 4.86-4.55 (3.5H, m), 4.45-4.25 (1.5H, m), 3.40-3.20 (1H, m), 3.20-2.70 (2H, m), 2.65-2.40 (1H, m), 2.34 (3H, s), 2.30-1.70 (5H, m), 1.65-1.40 (2H, m). Anal. Calcd for $C_{29}H_{32}N_4O_7$: C, 62.66; H, 5.95; N, 10.08. Found: C, 62.91; H, 6.00;

N, 9.70. MS (ES^+) 550 (M^+ + 2, 43%), 549 (M^+ + 1, 100), 374 (3), 280 (4), 279 (20), 118 (5).

[1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-[4-(phenylacetamido)benzamido]-6H-pyridazino[1,2-a][1,2]diazepin-1-carboxamide (213s), was isolated as the anti-isomer as a white foamy solid (0.64g, 77%): mp. 137-41°C; $[\alpha]_D^{21}$ -48.2° (c 0.05, CH_3OH); IR (KBr) 3477, 3314, 1791, 1659, 1599, 1529, 1499, 1406, 1256, 1122; ^1H NMR (D_6-DMSO) δ 10.45 (1H, s), 8.76 (1H, d), 8.50 (1H, d), 7.86 (2H, d), 7.69 (2H, d), 7.41-7.20 (10H, m), 5.43 (1H, s), 5.08-4.98 (1H, m), 4.90-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.67 (2H, s), 3.40-3.20 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.39 (1H, dd), 2.30-2.00 (3H, m), 2.00-1.75 (2H, m), 1.70-1.40 (2H, m). Anal. Calcd for $C_{36}H_{37}N_5O_8 \cdot 0.5H_2O$: C, 63.90; H, 5.66; N, 10.35. Found: C, 63.68; H, 5.67; N, 10.24. MS (ES^+) 669 (M^+ + 2, 40%), 668 (M^+ + 1, 100), 640 (12), 435 (18), 425 (23), 403 (33), 328 (17), 302, (32), 274 (22), 197 (16), 138 (17).

[1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-[4-(3-methylbutan-1-oylamino)benzamido]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213t), was isolated as a white foamy solid (0.63g, 80%): mp. 159-64°C; $[\alpha]_D^{21}$ -37.0° (c 0.05, CH_3OH); IR (KBr) 3463, 3321, 1790, 1680, 1658, 1650, 1644, 1595, 1525, 1501, 1408, 1251, 1113, 933; ^1H NMR (D_6-DMSO) δ 10.13 (1H, s), 8.76 (1H, d), 8.48 (1H, d), 7.85 (2H, d), 7.68 (2H, d),

7.40-7.25 (5H, m), 5.43 (1H, s), 5.08-4.95 (1H, m), 4.92-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.40-3.20 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.39 (1H, dd), 2.35-2.00 (6H, m), 2.00-1.75 (2H, m), 1.70-1.40 (2H, m), 0.93 (6H, d). Anal. Calcd for $C_{33}H_{39}N_5O_8 \cdot 0.5H_2O$: C, 61.67; H, 6.27; N, 10.90. Found: C, 61.49; H, 6.24; N, 10.86. MS (ES^+) 635 (M^+ + 2, 39%), 634 (M+ + 1, 100), 484 (10), 427 (9), 274 (18), 268 (37), 204 (19), 117 (13).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(3,4,5-trimethoxybenzoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213u), was isolated as a white solid (81%): mp. 120-132°C; IR (KBr) 3361-3334, 1792, 1659, 1585, 1536, 1499, 1457, 1416, 1340, 1236, 1126, 989; ^{1}H NMR ($CDCl_3$) δ 7.39-7.29 (6H, m), 7.12 (1H, s), 7.03 (1H, s), 6.92, 6.83, 6.48 (approx 3H, 3d, J = 8.1, 7.5, 8.1), 5.57 (d, J = 5.3), 5.27 (1H, s), 5.23-5.06, 4.91-4.71, 4.64-4.43, (6H, 3m), 3.92, 3.91, 3.89, 3.88 (9H, 4s), 3.32-2.70, 2.52-2.08, 1.91, 1.63 (1H, 4m).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(naphth-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213v), was isolated as a white solid (78%): mp. 121-7°C; IR (KBr) 3534-3331, 1791, 1659, 1528, 1420, 1256, 1122; ^{1}H NMR ($CDCl_3$) δ 8.34-8.29 (1H, m), 7.98-7.87 (2H, m), 7.68-7.45 (4H, m), 7.34-7.24 (5H, m), 7.04 (d, J = 6.8), 6.78 (d, J = 7.8), 6.66 (d, J = 7.7), 6.48 (2H, d, J = 7.5)5.56 (d, J = 5.4), 5.15

(1H, s), 5.30-5.14, 5.0, 4.89 (d, J = 11.2), 4.71-4.41 (6H), 3.18-2.80, 2.50-2.27, 2.08-1.60 (11H, 3m).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(4-hydroxy-3,5-dimethylbenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213w), was isolated as a mixture of diastereoisomers (65/35) as a white solid (0.9g, 65%): mp. 110-115°C (decomp.); IR (KBr) 3409, 2945, 1792, 1658, 1606, 1534, 1486, 1420, 1330, 1276, 1209, 1122, 980, 960; ^{1}H NMR ($CDCl_3$) δ 7.66 (0.35H, d, J = 6.9), 7.46-7.20 (7H, m), 6.93 (0.35H, d, J = 7.7), 6.85 (0.65H, d, J = 7.6), 6.73 (0.65H, d, J = 7.6), 5.96 (0.35H, bs), 5.85 (0.65H, bs), 5.56 (0.65H, d, J = 5.2), 5.28 (0.35H, bs), 5.20-4.98 (2H, m), 4.96-4.40 (4H, m), 3.28-2.55 (3H, m), 2.53-2.32 (1H, m), 2.23 (6H, 2s), 2.03-1.40 (7H, m). MS (ES^-) 577, (ES^+) 579.

[1*S*,9*S*(2R*S*,3*S*)] 9-[4-(Acetylamino)benzoylamino]-N-(2-benzyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboximide (213x), was isolated as a colourless poweder (691mg, 86%): mp. 150-70°C; $[\alpha]_D^{22}$ -10.1° (c 0.10, Me_2CO); IR (KBr) 3313, 1791, 1679, 1654, 1597, 1528, 1501, 1457, 1407, 1371, 1315, 1255, 1184, 1122, 933; ^{1}H NMR (d6-DMSO) δ 8.75 (1H, d), 8.47 (1H, d), 7.84 (2H, d), 7.66 (2H, d), 7.35 (5H, m), 5.43 (1H, s), 5.06-5.00 (1H, m), 4.90-4.64 (3H, m), 4.46-4.26 (2H, m), 3.16-2.86 (2H, m), 2.45-2.05 (5H, m), 2.07 (3H, s), 2.00-1.84 (2H, m), 1.68-1.56 (2H, m); Anal. Calcd for $C_{30}H_{33}N_5O_8 \cdot H_2O$: C, 59.11; H, 5.79; N,

11.49. Found: C, 59.38; H, 5.66; N, 11.31; M.S. (ES^+) 614 (100%), 592 (M^++1.66).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (415), was prepared by a similar method as compound **214e** to afford a white solid (297mg, 84%): mp. 158-62°C; $[\alpha]_D^{24}$ -109.5° (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 1783,1659, 1650, 1538, 1486, 1439, 1257, 1037; ^1H NMR (CD_3OD) δ 7.48 (1H, dd), 7.35 (1H, d), 6.88 (1H, d), 6.03 (2H, s), 5.25-5.15 (1H, m), 5.02-4.90 (1H, m), 4.63-4.45 (2H, m), 4.30-4.20 (1H, m), 3.57-3.30 (1H, m), 3.20-3.05 (1H, m), 2.75-2.10 (5H, m), 2.10-1.60 (4H, m). MS (ES^+) 488 (M+, 25%), 487 (M^+ - 1, 100), 443 (8), 387 (3), 315 (5), 150 (6), 127 (5), 113 (8). Accurate mass calculated for $C_{22}H_{25}N_4O_9$ (MH^+): 489.1621. Found 489.1648.

[3*S*(1*S*,9*S*)] 3-{9-[(3-Acetamido)benzamido]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-oxobutanoic acid (450), was prepared by a similar method as compound **214e** to afford a white foamy solid (378mg, 94%): mp. 175-9°C; $[\alpha]_D^{22}$ -91.7° (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 3319, 1659, 1590, 1553, 1427, 1260; ^1H NMR (CD_3OD) δ 8.01 (1H, d), 7.74 (1H, dd), 7.58 (1H, d), 7.45-7.35 (1H, m), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.60-4.45 (2H, m), 4.30-4.20 (1H, m), 3.55-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-2.20 (5H, m), 2.14 (3H, s), 2.20-1.60 (4H). Anal. Calcd for $C_{23}H_{27}N_5O_8 \cdot 1.5H_2O$: C, 52.27; H, 5.72; N, 13.25. Found:

C, 52.31; H, 5.86; N, 12.85. MS (ES^+) 501 (M+, 26%), 500 (M^+ - 1, 100), 328 (2), 149 (3), 113 (3).

[3*S*(1*S*,9*S*)] 3-[4-(Hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (456), was prepared by a similar method as compound **214e** to afford a white solid (0.73g, 72%): mp. >260°C; $[\alpha]_D^{20}$ -66° (c 0.34, MeOH); IR (KBr) 3401, 2946, 1651, 1609, 1584, 1506, 1426, 1277, 1257, 1177; ^{1}H NMR (D_6-DMSO) δ 10.2 (1H, very bs), 9.17 (1H, bs), 8.65 (1H, s), 8.37 (1H, d, J 5.4), 7.81 (2H, d, J = 8.2), 6.87 (2H, d, J = 8.4), 5.24 (1H, m), 4.92-4.86 (1H, m), 4.41-4.32 (2H, m), 3.68-3.21 (3H, m), 3.12-2.79 (1H, m), 2.50-1.42 (7H, m). MS (ES^+) 459.

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(indol-2-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (475), was prepared by a similar method to that described for compound **214e** to afford a white solid (79%): mp. 150°C (softens) 190-210°C; $[\alpha]_D^{23}$ -97.5° (c 0.1, CH_3OH); IR (KBr) 3319, 1658, 1650, 1549, 1421, 1256; ^{1}H NMR (CD_3OD) δ 7.61 (1H, d, J = 8.0), 7.43 (1H, d, J = 8.1), 7.21 (2H, m), 7.05 (1H, m), 5.21 (1H, m), 5.07-4.77 (1H, m), 4.54 (2H, m), 4.23 (1H, m), 3.46 (1H, m), 3.14 (1H, m), 2.66-1.71 (9H, m). MS (ES^+, m/z), 482 (M^+ - 1, 100%).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(2-toluoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (404), was prepared by

a similar method as compound **214e** to afford a white solid (0.79g, 86%): mp. 156-9°C; $[\alpha]_D^{25}$ -119.7° (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 3387, 3309, 2956, 1785, 1659, 1650, 1535, 1422, 1278; ^1H NMR (CD_3OD) δ 7.46-7.15 (4H, m), 5.25-5.15 (1H, m), 5.02-4.90 (1H, m), 4.58-4.45 (2H, m), 4.30-4.20 (1H, m), 3.55-3.30 (1H, m), 3.20-3.05 (1H, m), 2.80-2.20 (4H, m), 2.41 (3H, s), 2.20-1.60 (5H, m). MS (ES^+) 458 (M+, 27%), 457 (M^+ - 1, 100), 413 (13), 339 (8), 285 (5), 134 (6), 127 (11). Accurate mass calculated for $C_{22}H_{27}N_4O_7$ (MH^+): 459.1880. Found 459.1854.

[3*S*(1*S*,9*S*)] 3-{6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-[4-(phenylacetamido)benzamido]-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-oxobutanoic acid (486), was prepared by a similar method as compound **214e** to afford a white solid (325mg, 89%): mp. 165-9°C; $[\alpha]_D^{22}$ -69.1° (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 3318, 1658, 1599, 1530, 1505, 1407, 1258; ^1H NMR (CD_3OD) δ 7.85 (2H, d), 7.69 (2H, d), 7.38-7.20(5H, m), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.57-4.45 (2H, m), 4.30-4.20 (1H, m), 3.70 (2H, s), 3.55-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-1.60 (9H, m). Anal. Calcd for $C_{29}H_{31}N_5O_8 \cdot 1.5H_2O$: C, 57.61; H, 5.67; N, 11.58. Found: C, 57.81; H, 5.74; N, 11.47. MS (ES^+) 577 (M+, 33%), 576 (M^+ - 1, 100), 502 (2).

[3*S*(1*S*,9*S*)] 3-{6,10-Dioxo-9-[4-(3-methylbutan-1-oylamino)benzamido]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-oxobutanoic acid (487), was prepared by a similar

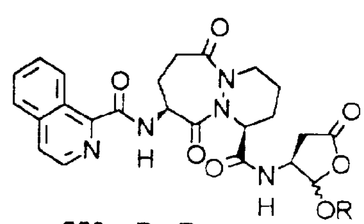
method as compound **214e** to afford a white foamy solid (335mg, 93%): mp. 176-80°C; $[\alpha]_D^{22}$ -88.0° (c0.1, CH_3OH); IR (KBr) 3700-2500 (br), 3321, 2960, 1781, 1660, 1597, 1529, 1407, 1258, 1187; ^1H NMR (CD_3OD) δ 7.86 (2H, d), 7.69 (2H, d), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.60-4.45 (2H, m), 4.30-4.20 (1H, m), 3.57-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-1.60 (12H, m), 1.00 (6H, d). Anal. Calcd for $C_{26}H_{33}N_5O_8 \cdot H_2O$: C, 55.61; H, 6.28; N, 12.45. Found: C, 56.00; H, 6.37; N, 12.15. MS (ES^+) 543 (M+, 31%), 542 (M^+ - 1, 100), 498 (2), 468 (3).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(3,4,5-trimethoxybenzoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (417), was prepared by a similar method to that described for compound **214e** to afford a white solid (0.63g, 92%): mp. 145-155°C (approx., not sharp); $[\alpha]_D^{27}$ -114.6° (c 0.11, CH_3OH); IR (KBr) 3327, 1658, 1586, 1548, 1501, 1416, 1341, 1238, 1126; ^1H NMR (CD_3OD) δ 7.22 (2H, s), 5.21 (1H, m), 5.00 (1H, m), 4.56, 4.49 (2H, 2m), 4.25 (1H, m), 3.88 (6H, s), 3.80 (3H, s), 3.55-3.43 (1H, m), 3.12 (1H, m), 2.71-1.70 (9H, m). Anal. Calcd for $C_{24}H_{30}N_4O_{10} \cdot 2H_2O$: C, 50.52; H, 6.01; N, 9.82. Found: C, 50.49; H, 6.05; N, 9.68. MS (ES^+, m/z) 533 (M^+ - 1, 100%).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(naphth-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (408), was prepared by a similar method to that described for compound **214e** to afford a

white solid (73%): mp. 157-165°C (not sharp); $[\alpha]_D^{27}$ -140.5° (c 0.1, CH_3OH); IR (KBr) 3325, 1658, 1531, 1420, 1278, 1257; ^1H NMR (CD_3OD) δ 8.33-8.28 (1H, m), 8.01-7.78 (2H, m), 7.71 (1H, d, J = 6.0), 7.59-7.52 (3H, m), 5.27 (1H, m), 5.12-5.03 (1H, m), 4.55 (2H, m), 4.25 (1H, m), 3.64-3.43 (1H, m), 3.24-3.12 (1H, m), 2.80-1.67 (9H, m). Anal. Calcd for $C_{25}H_{26}N_4O_7 \cdot 2H_2O$: C, 56.60; H, 5.70; N, 10.56. Found: C, 56.70; H, 5.80; N, 10.33. MS (ES^+, m/z), 493 (M^+ - 1, 100%).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-4-(hydroxy-3,5-dimethylbenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (214w), was prepared by a similar method as compound **214e** to afford 210mg (62%) of a white solid: mp. >260°C; $[\alpha]_D^{20}$ -93° (c 0.20, MeOH); IR (KBr) 3401, 2948, 1651, 1604, 1559, 1486, 1421, 1325, 1276, 1210; ^1H NMR (D_6-DMSO) δ 9.39 (1H, bs), 8.29 (1H, d, J = 5.9), 7.55 (2H, s), 6.64 (1H, d, J = 6.1), 5.79 (1H, s), 5.25-5.21 (1H, m), 1.90-1.82 (1H, m), 4.41-3.69 (2H, m), 3.47-3.20 (3H, m), 2.97-2.91 (1H, m), 2.23 (6H, s), 2.25-1.60 (7H, m).



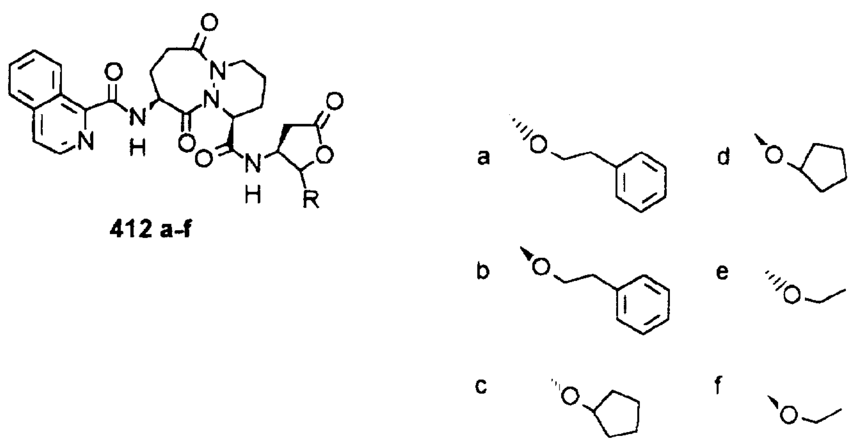
550q R= Et

213y R= Bn

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-

octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550q), was synthesized via methods used to prepare **213e** to afford **550q**.

[1*S*,9*S*(2*RS*,3*S*)] **N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213y)**, was synthesized via methods used to prepare **213e** to afford **213y**.



412 a-f

[1*S*,9*S*(2*S*,3*S*)] **N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide**, **(412a)** was synthesized via methods used to prepare **550q** using **513a-1** to afford **412a**.

[1*S*,9*S*(2*R*,3*S*)] **N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide**, **(412b)** was synthesized via

methods used to prepare **550q** using **513a-2** to afford **412b**.

[1*S*,9*S*(2*S*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412c) was synthesized via methods used to prepare **550q** using **513b-1** to afford **412c**.

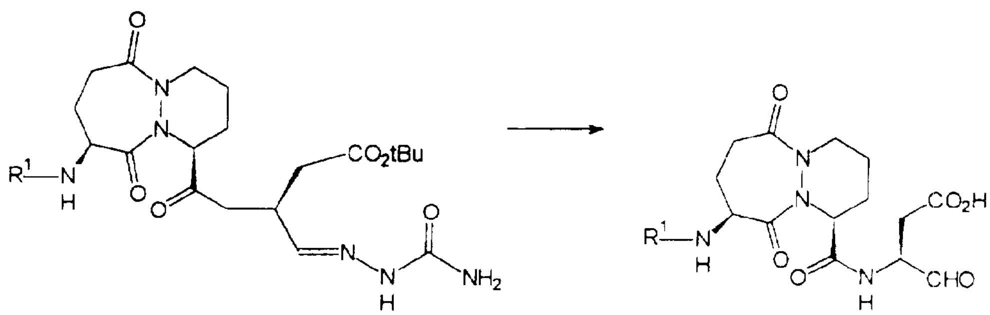
[1*S*,9*S*(2*R*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412d) was synthesized via methods used to prepare **550q** using **513b-2** to afford **412d**: ^{1}H NMR ($CDCl_3$) δ 9.5 (1H, d), 8.9 (1H, d), 8.5 (1H, d), 7.9-7.8 (2H, m), 7.8-7.65 (2H, m), 6.55 (1H, d), 5.55 (1H, d), 5.25-5.1 (2H, m), 4.75-4.65 (1H, m), 4.65-4.6 (1H, m), 4.4-4.3 (1H, m), 3.25-3.15 (1H, m), 3.15-3.05 (1H, m), 2.95-2.8 (2H, m), 2.55-2.4 (2H, m), 2.15-1.5 (14H, m).

[1*S*,9*S*(2*S*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (412e) was synthesized via methods used to prepare **550q** using **513f-1** to afford **412e**.

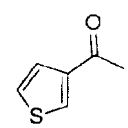
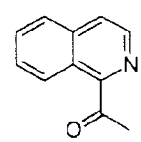
[1*S*,9*S*(2*R*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-

carboxamide, (412f) was synthesized via methods used to prepare **550q** using **513f-2** to afford **412f**.

Compounds **410** and **412** were prepared via methods used to prepare **605** from **604**.



502y, 502z **410, 412**

compound	R^1
502y, 410	
502z, 412	

[3*S*(1*S*,9*S*)] 3-[(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-9-(thiophene-3-yl-carbonylamino)-1-carboxamido]-4-oxobutanoic acid (410), was purified by flash chromatography (5-25% methanol in dichloromethane) to give 296mg (94%) of a colourless solid: mp. 90-200°C; IR (KBr) 3338, 3096, 2950, 1787, 1726, 1657, 1546, 1420, 1279, 1258, 1125, 1092, 984,

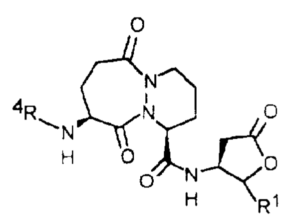
933; ^1H NMR (CD_3OD) δ 8.41 (1H, d), 8.13 (1H, d), 7.54-7.41 (3H, m), 7.20 (1H, d), 5.19-5.11 (1H, m), 4.54-4.30 (1H, m), 3.27 (1H, m), 3.18-3.03 (1H, m), 2.81-2.64 (2H, m), 2.56-1.59 (7H, m). Anal. Calcd for $C_{19}H_{22}N_4O_7S \cdot 2.5H_2O$: C, 46.05; H, 5.49; N, 11.31. Found: C, 46.36; H, 5.25; N, 11.10. MS (ES^+) 449 (M - 1, 80%), 113 (100). Accurate mass calculated for $C_{19}H_{23}N_4O_7S$ (MH^+): 451.1287. Found: 451.1295.

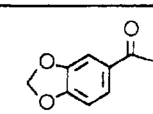
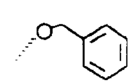
[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (412) was prepared by a similar method to that described for compound **605** to afford a white glassy solid (69%): mp. 138-141°C; $[\alpha]_D^{23}$ -105.5° (c 0.5, CH_2Cl_2); IR (KBr) 3375, 1787, 1659, 1515, 1421, 1278, 1256; ^1H NMR ($CDCl_3$) δ 9.32 (1H, m), 8.79 (1H, m), 8.47 (1H, m), 7.86-7.64 (4H, m), 5.31, 5.18, 4.59, 4.37 (4 or 5H, m), 3.55-2.76, 2.49-2.39, 2.05, 1.65 (11H, 4m). Anal. Calcd for $C_{24}H_{25}N_5O_7 \cdot 1.5H_2O$: C, 55.17; H, 5.40; N, 13.40. Found: C, 54.87; H, 5.22; N, 13.15. MS (ES^+, m/z) 494 (M^+ - 1, 100%).

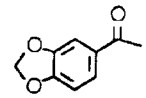
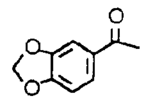
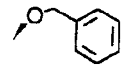
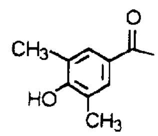
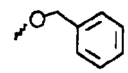
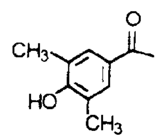
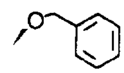
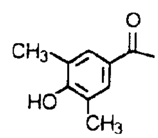
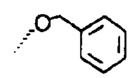
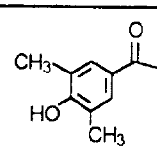
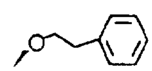
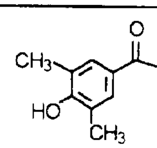
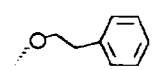
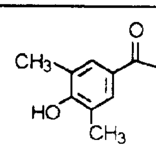
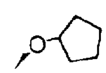
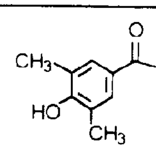
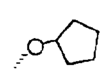
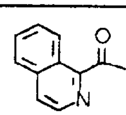
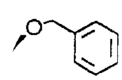
[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo—1,2,3,4,7,8,9,10-octahydro-9-(thiophene-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-carbonylamino)-1-carboxamido]-4-oxobutanoate semicarbazone (502y), was synthesized via methods used to prepare **604** from **603** to afford a pale cream powder: mp. 120-180°C; $[\alpha]_D^{23}$ -109° (c 0.18, CH_2Cl_2); IR (KBr) 3478, 3327, 1670, 1582, 1543, 1421, 1279, 1257, 1155; ^1H NMR ($CDCl_3$, CD_3OD) δ 8.04 (1H, m), 7.49 (1H, m), 7.38 (1H, m), 7.17 (1H, m),

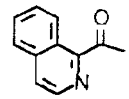
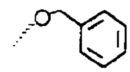
5.17-5.01 (2H, m), 4.86 (1H, m), 4.61-4.50 (1H, m), 3.45-3.29 (2H, m), 3.21-3.03 (1H, m), 2.79-2.54 (3H, m), 2.43-2.33 (1H, m), 2.11-1.66 (5H, m), 1.44 (9H, s). Anal. Calcd for $C_{24}H_{33}N_7O_7S{\bullet}H_2O$: C, 49.56; H, 6.07; N, 16.86; S, 5.51. Found: C, 49.51; H, 5.93; N, 16.31; S, 5.17. MS (ES^+) 586 (100%), 564 (M^+ + 1, 1.59). Accurate mass calculated for $C_{24}H_{34}N_7O_7S$ (MH^+): 564.2240. Found: 564.2267.

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoate semicarbazone (502z), was prepared by a similar method to that described for compound **604** to afford a pale yellow solid (90%): mp. 142-145°C; $[\alpha]_D^{24}$ -136.5° (c 0.06, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 9.51-9.46 (1H, m), 9.11 (1H, s), 8.83 (1H, d, J = 7.8), 8.53 (1H, d, J = 5.5), 7.89-7.83 (2H, m), 7.77-7.65 (2H, m), 7.55 (1H, d, J = 7.2), 7.18 (1H, d, J = 2.7), 5.26-5.12 (2H, m), 4.87 (1H, m), 4.59 (1H, m), 3.25-3.12 (2H, m), 2.95-2.76 (2H, m), 2.59-2.38, 2.18-1.94, 1.70 (5H, 3m), 1.44 (9H, s).



compound	R^4	R^1
415a		

compound	R^4	R^1
415b		
415c		
214w-1		
214w-2		
214w-3		
214w-4		
214w-5		
214w-6		
214w-7		
412g		

compound	R^4	R^1
412h		

[1*S*,9*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (415a) was synthesized via methods used to prepare **550q** to afford **415a.**

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxy benzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (415b) was synthesized via methods used to prepare **550q** to afford **415b.**

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxy benzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (415c) was synthesized via methods used to prepare **550q** to afford **415c.**

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-1) was synthesized via methods used to prepare **550q** to afford **214w-1.**

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-

1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-2) was synthesized via methods used to prepare **550q** to afford **214w-2.**

[1*S*,9*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-3) was synthesized via methods used to prepare **550q** to afford **214w-3.**

[1*S*,9*S*(2*R*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-4) was synthesized via methods used to prepare **550q** to afford **214w-4.**

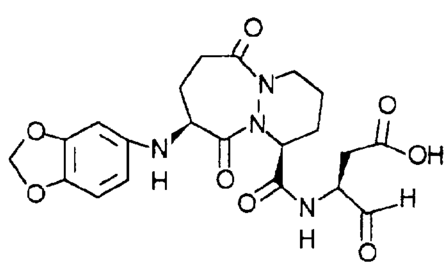
[1*S*,9*S*(2*S*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-5) was synthesized via methods used to prepare **550q** to afford **214w-5.**

[1*S*,9*S*(2*R*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-6) was synthesized via methods used to prepare **550q** to afford **214w-6.**

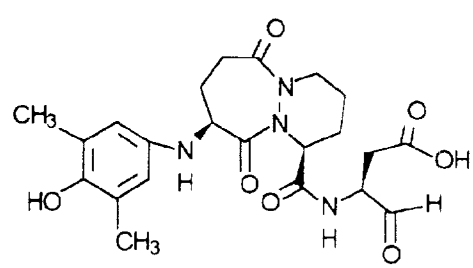
[1*S*,9*S*(2*S*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-7) was synthesized via methods used to prepare **550q** to afford **214w-7**.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (412g) was synthesized via methods used to prepare **550q** to afford **412g**.

[1*S*,9*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (412h) was synthesized via methods used to prepare **550q** to afford **412h**.



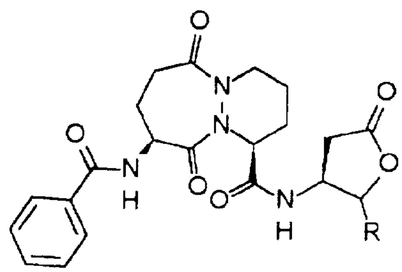
415



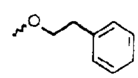
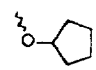
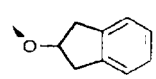
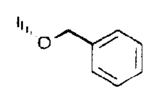
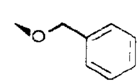
214w

[3*S*(1*S*,9*S*)]3-(9-(4,5-Methylenedioxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (415), was synthesized by the method used to prepare **2002** from **2001** to afford **415**.

[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichloro-4-hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214w), was synthesized by the method used to prepare **2002** from **2001** to afford **214w**.



2100k-o

compound	R
2100k	
2100l	
2100m	
2100n	
2100o	

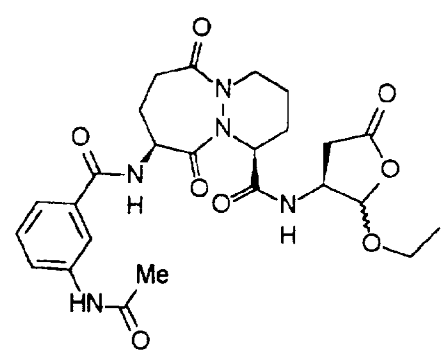
[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo—1,2,3,4,7,8,9,10-octahydro-N-(2-phenethyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100k), was prepared by a similar method as compound **213e** to afford a mixture of diastereoisomers (75/25) as a white solid (258mg, 83%): mp. 101°C; $[\alpha]_D^{25}$ -96° (c 0.2, CH_2Cl_2); IR (KBr) 3328, 2935, 2978, 1732, 1669, 1603, 1483, 1450, 1414, 1237, 1155, 1082, 989, 755; ^1H NMR ($CDCl_3$) δ 7.84-7.80 (2H, m), 7.54-7.17 (8H, m), 7.06-6.99 (1H, m), 6.25 (1H, d, J = 7.9H), 5.41 (0.75H, d, J = 5.4H), 5.31 (0.25H, bs), 5.23-5.09 (1H, m), 4.93-4.87 (1H, m), 4.68-4.51 (2H, m), 4.40-4.33 (0.25H, m), 4.24-4.14 (0.75H, m), 3.95-3.70 (1H, m), 3.30-3.13 (1H, m), 3.14-2.78 (5H, m), 2.47-2.21 (2H, m), 2.05-1.50 (5H, m). Anal. Calcd for $C_{29}H_{32}N_4O_7 \cdot 0.5H_2O$: C, 62.47; H, 5.97; N, 10.05. Found: C, 62.17; H, 5.83; N, 9.97. MS (ES^+) 549.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzamido-N-(2-cyclopentyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo—1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100l), was prepared by a similar method as **213e**, (74%) as a colourless solid: mp. 172-80°C; $[\alpha]_D^{23}$ -91.5° (c 0.1, CH_2Cl_2); IR (KBr) 3290, 1792, 1677, 1657, 1642, 1544, 1425, 1280, 1259, 1124, 977; ^1H NMR ($CDCl_3$) δ 7.80 (2H, m), 7.46 (3.5H, m), 7.00 (1H, d, J = 6.7), 6.48 (0.5H, d, J = 7.9), 5.55 (0.5H, d, J = 5.3), 5.19 (2H, s + m), 4.93 (0.5H, m), 4.62 (1.5H, m), 4.34 (1H, m), 4.18 (0.5H, m), 3.28-2.70 (4H, m), 2.49-2.29 (2H, m), 205-1.48 (15H, m).

[1*S*,9*S*(2*R*,3*S*)] 9-Benzamido-6,10-dioxo–N-[2-(2-indanyloxy)-5-oxo-tetrahydrofuran-3-yl]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100m), was prepared by a similar method as **213e**, (76%) as a colourless solid: mp. ~140°C, remelts 187-9°C; $[\alpha]_D^{23}$ -96.9° (c 0.11, CH_2Cl_2); IR (KBr) 3507, 3308, 3251, 1772, 1660, 1641, 1566, 1545, 1457, 1424, 1346, 1326, 1302, 1275, 1258, 1136, 1085, 1018, 981; ^{1}H NMR ($CDCl_3$) δ 7.78 (2H, m), 7.53 (3H, m), 7.19 (4H, m), 6.91 (1H, d, J = 7.4), 6.27 (1H, d, J = 7.6), 5.66 (1H, d, J = 5.3), 5.10 (1H, m), 4.96 (1H, m), 4.75 (2H, m), 4.52 (1H, m), 3.08 (3H, m), 3.03-2.71 (5H, m), 2.48-2.31 (2H, m), 1.90-1.40 (4H, m), 1.22 (1H, m).

[1*S*,9*S*(2*S*,3*S*)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo–1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100n), was prepared by a similar method to that described for compound **213e** to afford a white glassy solid (76%): mp. 112-5°C; $[\alpha]_D^{23}$ -62.0° (c 0.1, CH_2Cl_2); IR (KBr) 3305, 1789, 1677, 1665, 1535, 1422, 1279, 1256, 1119, 942, 700; ^{1}H NMR ($CDCl_3$) δ 7.84 (2H, m), 7.58-7.27 (9H, m), 6.99 (1H, d, J = 7.8), 5.23 (1H, s), 5.23-5.11 (1H, m), 4.89 (1H, m), 4.76 (1H, d, J = 11.3), 4.55 (1H, d, J = 11.4), 4.58-4.43 (2H, m), 3.30-2.96, 2.81-2.69, 2.46-2.37, 2.16-1.66 (10H, 4m), 2.27 (1H, d, J = 17.8). Anal. Calcd for $C_{28}H_{30}N_4O_7 \cdot 0.5H_2O$: C, 61.87; H, 5.75; N, 10.32. Found: C, 61.88; H, 5.70; N, 10.33. MS (ES^+, m/z) 535 (M^+ + 1, 100%).

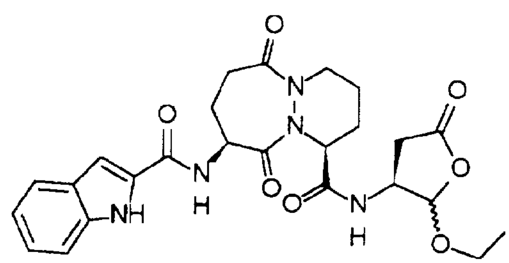
[1*S*,9*S*(2*R*,3*S*)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100o), (containing about 7% of (2*S*)), was prepared by a similar method to that described for compound **213e** to afford a white glassy solid (81%): mp. 115-7°C; $[\alpha]_D^{23}$ -121.8° (c 0.11, CH_2Cl_2); IR (KBr) 3326, 1792, 1659, 1535, 1421, 1278, 1257, 1124, 978; ^1H NMR ($CDCl_3$) δ 7.82 (2H, m), 7.58-7.24 (8H, m), 6.90 (1H, d, J = 7.3), 6.49 (1H, d, J = 7.7), 5.57 (1H, d, J = 5.5), 5.11 (2H, m), 4.91 (1H, d, J = 11.4), 4.57 (1H, d, J = 11.1), 4.81-4.68 (1H, m), 4.65-4.54 (1H, m), 3.18-2.71 2.52-2.30, 2.05-1.62 (11H, 3m). Anal. Calcd for $C_{28}H_{30}N_4O_7 \cdot 0.5H_2O$: C, 61.87; H, 5.75; N, 10.32. Found: C, 61.70; H, 5.71; N, 10.15. MS (ES^+, m/z) 535 (M^+ + 1, 94.3%), 557 (100%).



550n

[1*S*,9*S*(2*RS*,3*S*)] 9-(3-Acetamido)benzoylamino-6,10-dioxo-N-(2-ethoxy-5-oxo-tetrahydrofuran-3-yl)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550n), was prepared by a similar method as compound **213e** to

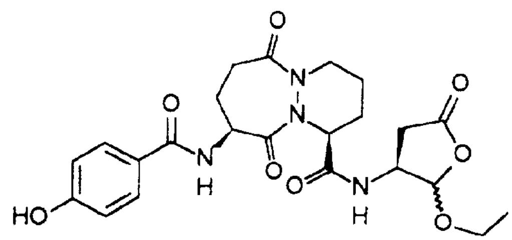
afford a mixture of diastereoisomers (65/35) as a tan powder (390mg, 28%): mp. 139-145°C; $[\alpha]_D^{23}$ -104° (c 0.2, MeOH); IR (KBr) 3318, 2405, 2369, 1792, 1660, 1591, 1549, 1484, 1422, 1257, 1117; ^{1}H NMR (D_6-DMSO) δ 10.1 (1H, s), 8.80 (0.65H, d, J = 6.6), 8.58 (0.35H, d, J = 6.6), 8.59 (1H, d, J = 7.0), 8.06 (1H, bs), 7.83-7.79 (1H, m), 7.61-7.57 (1H, m), 7.47-7.39 (1H, m), 5.61 (0.35H, d, J = 5.0), 5.37 (0.65H, bs), 5.17-5.14 (0.35H, m), 5.08-5.06 (0.65H, m), 4.92-4.86 (1H, m), 4.67-4.61 (0.35H, m), 4.47-4.41 (0.65H, m), 4.28-4.11 (1H, 2m), 3.80-3.59 (2H, m), 3.23-2.75 (3H, m), 2.61-1.48 (7H, m), 2.10 (3H, s), 1.25 and 1.17 (3H, 2t, J = 5.8). MS (ES^+) 528.



550o

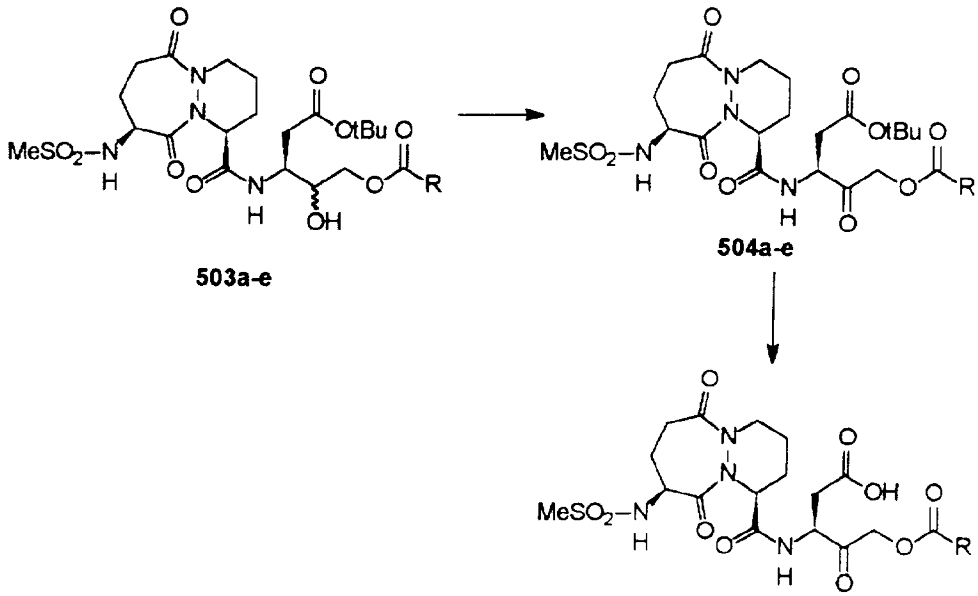
[1*S*,9*S*(2*RS*,3*S*)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-9-(2-indoloylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550o), was synthesized by a similar method as compound **213e** to afford a colourless solid (1.071g, 80%): mp. 155-70°C; $[\alpha]_D^{22}$ -75.8° (c 0.26, CH_2Cl_2); IR (KBr) 3314, 2941, 1791, 1658, 1545, 1420, 1341, 1312, 1252, 1181, 1118, 939, 749; ^{1}H NMR ($CDCl_3$) δ 9.45 (0.5H, s), 9.34 (0.5H, s), 7.68-7.62 (1H, m), 7.49-7.39 (2H, m), 7.33-7.26

(1H, m), 7.18-7.03 (3H, m), 5.49 (0.5H, d), 5.30 (0.5 H, s), 5.26-5.13 (1H, m), 4.90-4.83 (0.5H, m), 4.76-4.49 (1H, m), 4.42-4.35 (0.5H, m), 3.97-3.74 (1H, m), 3.72-3.53 (1H, m), 3.35-2.64 (4H, m), 2.50-2.37 (1H, m), 2.20-1.82 (5H, m), 1.69-1.50 (2H, m), 1.30-1.19 (3H, m).



550p

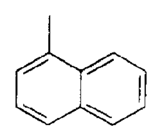
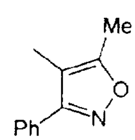
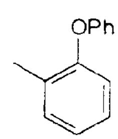
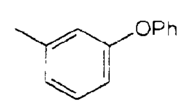
[1*S*,9*S*(2*RS*,3*S*)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-9-(4-hydroxybenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550p), was prepared by a similar method as compound **213e** to afford a mixture of diastereoisomers as a white foam (820mg, 47%): $[\alpha]_D^{24}$ -75° (c 0.16, CH_2Cl_2); IR (KBr) 3401, 2937, 1791, 1657, 1609, 1539, 1505, 1423, 1277, 1177, 1118; ^{1}H NMR ($CDCl_3$) δ 8.07-8.05 (1H, m), 7.67 (2H, d, J = 7.9), 7.38-7.29 (2H, m), 6.80 (2H, d, J = 8.5), 5.49 (0.5H, d, J = 4.6), 5.23 (0.5H, bs), 5.24-5.20 (1H, m), 5.12-5.08 (1H, m), 4.68-4.29 (2H, m), 3.92-3.45 (3H, m), 3.32-2.30 (2H, m), 2.80-1.56 (11H, m), 1.21 (3H, t, J = 7.0H).

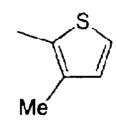


503a-e

504a-e

286, 505b-e

compound	R
503a 504a 286	
503b 504b 505b	
503c 504c 505c	
503d 504d 505d	

503e **504e** **505e**	

[3*S*,4*R*(1*S*,9*S*)] t-Butyl 3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxy-5-(1-naphthoyloxy)pentanoate (503a), was prepared from **212b** and (3*S*,4*R*) t-butyl (N-allyloxycarbonyl)-3-amino-4-hydroxy-5-(1-naphthoyloxy)pentanoate by the method described for **(213e)** to afford 533mg (81%) of an off-white foam: $[\alpha]_D^{22}$ -81.4° (c 0.5, CH_2Cl_2); IR(KBr) 3342, 2976, 1719, 1664, 1328, 1278, 1246, 1153, 1137. ^1H NMR ($CDCl_3$) δ 8.86 (1H, d, J = 8.4), 8.21 (1H, dd, J = 1.3, 7.3), 8.03 (1H, d, J = 8.1), 7.88 (1H, d, J = 8.6), 7.66-7.45 (3H, m), 7.23 (1H, d, J = 8.6), 5.96 (1H, d, J = 9.2), 5.30 (1H, m), 4.59-4.33 (5H, m), 4.24 (1H, m), 3.96 (1H, brd), 3.29 (1H, m), 2.95 (1H, m), 2.93 (3H, s), 2.69-2.50 (3H, m), 2.36 (1H, m), 1.96 (4H, m), 1.62 (1H, m), 1.41 (9H, s). Anal. Calcd for $C_{31}H_{40}N_4O_{10}S \cdot 0.25H_2O$: C, 55.97; H, 6.14; N, 8.42. Found: C, 55.90; H, 6.11; N, 8.23. M.S. (ES^+) 683 (M+Na, 100%), 661 (M+1,39), 605 (78).

[3*S*(1*S*,9*S*)] t-Butyl 3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(1-naphthoyloxy)-4-oxopentanoate (504a), was synthesized from **503a** via method used to prepare **216e** from **215e** to afford 446mg (91%) of a colourless foam: $[\alpha]_D^{21}$ -111.6°

(c 0.5, CH_2Cl_2); IR (KBr) 3319, 2978, 2936, 1723, 1670, 1413, 1370, 1329, 1278, 1246, 1153. ^1H NMR ($CDCl_3$) δ 8.87 (1H, d, J = 8.9), 8.29 (1H, d, J = 7.2), 8.06 (1H, d, J = 8.3), 7.90 (1H, d, J = 8.2), 7.66-7.48 (3H, m), 7.37 (1H, d, J = 8.1), 5.61 (1H, d, J = 9.0), 5.31 (1H, m), 5.22 (1H, AB, J = 16.9), 5.09 (1H, AB, J = 16.92), 4.99 (1H, m), 4.65-4.43 (2H, m), 3.28 (1H, m), 2.96 (3H, s), 2.86 (2H, m), 2.59 (1H, m) 2.38 (1H, dd, J = 6.8, 13.2), 2.21-1.70 (6H, m), 1.45 (9H, s). Anal. Calcd for $C_{31}H_{38}N_4O_{10}S \cdot 0.25H_2O$. C, 56.14; H, 5.85; N, 8.45. Found: C, 56.11; H, 5.83; N, 8.29. M.S. (ES^+) 657 (M-1, 100%).

[3*S*(1*S*,9*S*)] 3-(6,10-Dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(1-naphthoyloxy)-4-oxopentanoic acid (286), was prepared from **504a** by the method described for **217** to afford 356mg (93%) of a white powder: mp 120-123°C; $[\alpha]_D^{23}$ -121° (c 0.194, CH_2Cl_2); IR (KBr) 3314, 2937, 1722, 1663, 1412, 1328, 1278, 1245, 1195, 1132. ^1H NMR (d6-DMSO) δ 12.63 (1H, brs), 8.94 (1H, d, J = 7.4), 8.78 (1H, d, J = 8.6), 8.26 (2H, m), 8.11 (1H, d, J = 8.0), 7.77-7.62 (4H, m), 5.28 (2H, s), 5.21 (1H, m), 4.82 (1H, m), 4.44-4.29 (2H, m), 3.31 (1H, m), 2.98 (3H, s), 2.98-2.86 (2H, m), 2.72 (1H, dd, J = 7.3, 16.9), 2.40 (1H, m), 2.24-1.84 (4H, m), 1.69 (2H, m). Anal. Calcd for $C_{27}H_{30}N_4O_{10}S \cdot H_2O$: C, 52.25; H, 5.20; N, 9.03. Found: C, 52.11; H, 4.97; N, 8.89. M.S. (ES^+) 601 (M-1, 100%).

[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-9-

(methanesulphonylamino)-1-carboxamido]-4-hydroxy-5-(5-methyl-3-phenylisoxazoyloxy)pentanoate (503b), was synthesized by a similar method as compound **213e**, to afford an off-white powder (671mg, 88%): mp. 90-120°C; IR (KBr) 3345, 2977, 1727, 1664, 1532, 1450, 1423, 1369, 1323, 1310, 1276, 1257, 1154, 1101, 990, 766; ^{1}H NMR ($CDCl_3$) δ 7.61-7.55 (2H, m), 7.51-7.42 (3H, m), 6.86 (1H, d), 5.69 (1H, d), 5.21 (1H, m), 4.64-4.38 (2H, m), 4.15-4.05 (3H, m), 3.84 (1H, s), 3.31-3.14 (2H, m), 2.97-2.87 (1H, m), 2.94 (3H, s), 2.76 (3H, s), 2.64-2.48 (3H, m), 2.39-2.29 (1H, m), 2.04-1.61 (5H, m). Anal. Calcd for $C_{31}H_{41}N_5O_{11}S{\cdot}H_2O$: C, 52.46; H, 6.11; N, 9.87; S, 4.52. Found: C, 52.34; H, 5.92; N, 9.56; S, 4.44. MS (ES^+) 714 (47%), 692 (M^+ + 1, 84), 636 (100).

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(5-methyl-3-phenylisoxazoyloxy)-4-oxopentanoate (504b), was synthesized by a similar method as compound **216b** to afford a colourless powder (601mg, 93%): mp. 75-115°C; $[\alpha]_D^{23}$ -104° (c 0.26, CH_2Cl_2); IR (KBr) 3324, 2977, 2935, 1730, 1670, 1525, 1452, 1422, 1369, 1317, 1276, 1256, 1222, 1155, 1107, 990, 766; ^{1}H NMR ($CDCl_3$) δ 7.68-7.61 (2H, m), 7.47-7.38 (3H, m), 7.32-7.24 (1H, m), 5.56 (1H, d), 5.36-5.24 (1H, m), 5.04 (1H, d), 4.88 (1H, d), 4.86-4.77 (1H, m), 4.64-4.39 (2H, m), 3.32-3.17 (1H, m), 2.97-2.85 (1H, m), 2.93 (3H, s), 2.76 (3H, s), 2.80-2.71 (1H, m), 2.65-2.49 (1H, m), 2.41-2.30 (1H, m), 2.12-1.61 (6H, m), 1.42 (9H, s). Anal. Calcd for $C_{31}H_{39}N_5O_{11}S{\cdot}H_2O$: C, 52.61; H, 5.84; N, 9.90; S, 4.53. Found: C, 52.94; H, 5.69; N, 9.72; S, 4.51.

MS (ES^+) 712 (31%), 707 (100), 690 (M^+ + 1, 41), 634 (55).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(5-methyl-3-phenylisoxazoyloxy)-4-oxopentanoic acid (505b), was synthesized by a similar method as compound **217** to afford a colourless powder (499mg, 96%): mp. 95-145°C; $[\alpha]_D^{22}$ -137° (c 0.12, MeOH); IR (KBr) 3323, 2936, 1732, 1665, 1529, 1452, 1421, 1312, 1275, 1256, 1221, 1183, 1153, 1135, 1101, 990; ^1H NMR (CD_3OD) δ 7.67-7.56 (2H, m), 7.49-7.38 (4H, m), 5.23-5.12 (1H, m), 5.02 (1H, d), 4.79-4.73 (1H, m), 4.52-4.34 (3H, m), 3.48-3.25 (2H, m), 3.03-2.85 (2H, m), 2.94 (3H, s), 2.74 (3H, s), 2.79-2.66 (1H, m), 2.52-2.38 (1H, m), 2.29-2.14 (1H, m), 2.04-1.70 (4H, m). Anal. Calcd for $C_{27}H_{31}N_5O_{11}S{\bullet}H_2O$: C, 49.77; H, 5.18; N, 10.75; S, 4.92. Found: C, 49.83; H, 5.01; N, 10.27; S, 4.84. MS (ES^+) 746 (42%), 632 (M - 1, 100), 386 (60). Accurate mass calculated for $C_{27}H_{32}N_5O_{11}S$ (MH^+): 634.1819. Found: 634.1807.

[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-hydroxy-5-(2-phenoxybenzoyloxy)pentanoate (503c), was synthesized by a similar method as compound **213e** to afford a colourless solid (446mg, 84%): IR (KBr) 3345, 2976, 2935, 1727, 1664, 1603, 1535, 1483, 1451, 1416, 1395, 1369, 1328, 1297, 1277, 1237, 1155, 1135, 1076, 990, 755; ^1H NMR ($CDCl_3$) δ 7.98-7.89 (1H, m), 7.55-7.45

(1H, m), 7.39-7.18 (3H, m), 7.14-7.07 (1H, m), 7.00-6.90 (3H, m), 6.75 (1H, d), 5.57-5.50 (1H, m), 5.21-5.09 (1H, m), 4.64-4.42 (2H, m), 4.36-4.12 (3H, m), 3.95-3.87 (1H, m), 3.39-3.18 (1H, m), 3.00-2.82 (1H, m), 2.95 (3H, s), 2.69-2.48 (3H, m), 2.42-2.28 (1H, m), 2.07-1.62 (6H, m), 1.42 (9H, s). Anal. Calcd for $C_{33}H_{42}N_4O_{11}S \cdot H_2O$: C, 54.99; H, 6.15; N, 7.77; S, 4.45. Found: C, 54.95; H, 5.95; N, 7.34; S, 4.20. MS (ES^+) 725 (26%), 720 (47), 703 (M^+ + 1, 34), 433 (100), 403 (89).

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(2-phenoxybenzoyloxy) pentanoate (504c), was synthesized by a similar method as compound **216e** to afford a colourless powder: mp. 85-100°C; $[\alpha]_D^{22}$ -91.3° (c 0.52, CH_2Cl_2); IR (KBr) 3328, 2978, 2935, 1732, 1669, 1603, 1524, 1483, 1450, 1396, 1369, 1296, 1276, 1237, 1155, 1132, 1082, 989, 755; ^1H NMR ($CDCl_3$) δ 8.03-7.98 (1H, m), 7.52-7.44 (1H, m), 7.37-7.07 (5H, m), 7.01-6.92 (3H, m), 5.52 (1H, d), 5.28-5.20 (1H, m), 5.06-4.84 (3H, m), 4.64-4.39 (2H, m), 3.32-3.14 (1H, m), 2.99-2.88 (1H, m), 2.94 (3H, s), 2.65-2.45 (2H, m), 2.39-2.29 (1H, m), 2.12-1.58 (6H, m), 1.40 (9H, s). Anal. Calcd for $C_{33}H_{40}N_4O_{11}S$: C, 56.56; H, 5.75; N, 8.00; S, 4.58. Found: C, 56.37; H, 5.84; N, 7.69; S, 4.37. MS (ES^+) 723 (30%), 718 (100), 701 (M^+ + 1, 23), 645 (59).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-

(2-phenoxybenzoyloxy)pentanoic acid (505c), was synthesized by a similar method as compound **217** to afford a colourless foam (252mg, 72%): mp. 90-125°C; $[\alpha]_D^{23}$ -133° (c 0.11, MeOH); IR (KBr) 3314, 2938, 1792, 1734, 1663, 1604, 1535, 1483, 1448, 1415, 1250, 1132, 756; ^{1}H NMR (D_6-DMSO) δ 8.81-8.76 (1H, m), 7.92 (1H, d), 7.68-7.54 (2H, m), 7.41-7.25 (3H, m), 7.16-6.91 (4H, m), 5.13-4.98 (2H, m), 4.72-4.63 (1H, m), 4.37-4.21 (2H, m), 2.92 (3H, s), 2.90-2.60 (3H, m), 2.35-2.26 (1H, m), 2.17-2.05 (2H, m), 1.99-1.80 (2H, m), 1.61-1.50 (1H, m).Anal. Calcd for $C_{29}H_{32}N_4O_{11}S \cdot 0.5H_2O$: C, 53.29; H, 5.09; N, 8.57; S, 4.90. Found: C, 53.57; H, 5.18; N, 8.32; S, 4.75. MS (ES^+) 643 (M - 1, 100%).

[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-hydroxy-5-(3-phenoxybenzoyloxy) pentanoate (503d), was synthesized by a similar method as compound **213e** to afford a colourless solid (563mg, 90%): IR (KBr) 3349, 2978, 2935, 1724, 1664, 1583, 1536, 1489, 1443, 1370, 1327, 1271, 1226, 1189, 1155, 1073, 990, 755; ^{1}H NMR ($CDCl_3$) δ 7.77 (1H, d), 7.67 (1H, m), 7.45-7.10 (6H, m), 7.00 (2H, d), 5.93-5.80 (1H, m), 5.36-5.30 (1H, m), 4.63-4.24 (5H, m), 4.15-4.09 (1H, m), 3.37-3.22 (1H, m), 2.98-2.74 (1H, m), 2.94 (3H, s), 2.70-2.47 (3H, m), 2.40-2.30 (1H, m), 2.15-1.60 (5H, m), 1.42 (9H, s). Anal. Calcd for $C_{33}H_{42}N_4O_{11}S \cdot H_2O$: C, 54.99; H, 6.15; N, 7.77; S, 4.45. Found: C, 54.60; H, 5.88; N, 7.49; S, 4.50. MS (ES^+) 725 (19%), 720 (91), 703 (M^+ + 1, 74), 647 (76), 629 (100), 433 (78).

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-phenoxybenzoyloxy) pentanoate (504d), was synthesized by a similar method as compound **216e** to afford a colourless powder (466mg, 85%): mp. 75-100°C; $[\alpha]_D^{22}$ -99.3° (c 0.60, CH_2Cl_2); IR (KBr) 3335, 2978, 2937, 1728, 1669, 1584, 1525, 1487, 1444, 1416, 1369, 1328, 1272, 1227, 1188, 1155, 989, 754; ^{1}H NMR ($CDCl_3$) δ 7.82-7.77 (1H, m), 7.66-7.65 (1H, m), 7.46-7.32 (4H, m), 7.26-7.10 (2H, m), 7.04-6.98 (2H, m), 5.68 (1H, d), 5.37-5.31 (1H, m), 5.11 (1H, d), 5.02-4.88 (2H, m), 4.66-4.42 (2H, m), 3.35-3.17 (1H, m), 2.98-2.89 (1H, m), 2.96 (3H, s), 2.84-2.78 (1H, m), 2.72-2.47 (1H, m), 2.42-2.32 (1H, m), 2.14-1.58 (6H, m), 1.43 (9H. s). Anal. Calcd for $C_{33}H_{40}N_4O_{11}S$: C, 56.56; H, 5.75; N, 8.00. Found: C, 56.36; H, 5.82; N, 7.71. MS (ES^+) 723 (56%), 718 (90), 701 (M^+ + 1, 36), 645 (100).

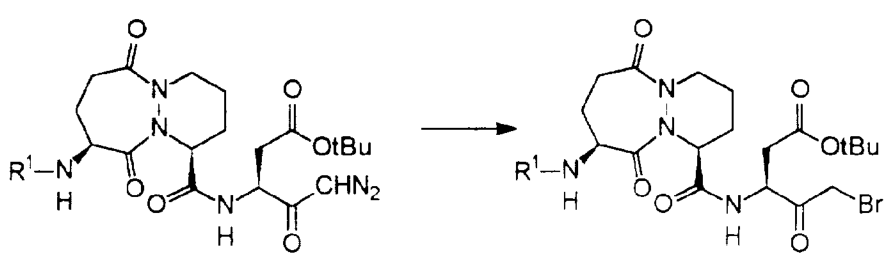
[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-phenoxybenzoyloxy)pentanoic acid (505d), was synthesized by a similar method as compound **217** to afford a colourless foam (353mg, 73%): mp. 80-115°C; $[\alpha]_D^{23}$ -138° (c 0.11, MeOH); IR (KBr) 3327, 2937, 1728, 1666, 1584, 1529, 1487, 1443, 1413, 1328, 1273, 1227, 1189, 1155, 1134, 989, 754; ^{1}H NMR (D_6-DMSO) δ 8.82 (1H, d), 7.76-7.72 (1H, m), 7.61-7.53 (2H, m), 7.48-7.32 (4H, m), 7.24-7.17 (1H, m), 7.11-7.06 (2H, m), 5.14-5.06 (3H, m), 4.73-4.64 (1H, m), 4.38-4.24 (2H, m), 2.92 (3H, s), 2.89-2.61 (3H, m), 2.38-2.27 (1H, m),

2.19-2.06 (2H, m), 2.02-1.79 (3H, m), 1.63-1.52 (1H, m). Anal. Calcd for $C_{29}H_{32}N_4O_{11}S \cdot 0.5H_2O$: C, 53.29; H, 5.09; N, 8.57; S, 4.90. Found: C, 53.24; H, 5.14; N, 8.34; S, 4.86. MS (ES^+) 643 (M - 1, 100%), 385 (62).

[3*S*,4*R*(1*S*,9*S*)] t-Butyl 5-(3-chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxypentanoate (503e), was prepared by a similar method to that described for compound **213e**, to afford an off white solid (70%): mp. 100-103°C; $[\alpha]_D^{25}$ -84.0° (c 0.05, CH_2Cl_2); IR (KBr) 3459-3359, 1722, 1664, 1514, 1368, 1328, 1278, 1247, 1155; ^1H NMR ($CDCl_3$) δ 7.52 (1H, m), 7.06-6.99 (2H, m), 5.69 (1H, d, J = 9.0), 5.23 (1H, m), 4.61-4.16 (6H, m), 3.36-3.19 (1H, m), 2.96 (3H, s), 2.67-2.49, 2.42-2.32, 2.06-1.89, 1.69 (10H, 4m), 1.43 (9H, s).

[3*S*(1*S*,9*S*)] t-Butyl 5-(3-chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (504e), was prepared by a similar method to that described for compound **216e**, to afford a white solid (98%): mp. 91-98°C; $[\alpha]_D^{25}$ -112.5°C (c 0.06, CH_2Cl_2); IR (KBr) 3453-3364, 1727, 1668, 1513, 1420, 1368, 1245, 1155; ^1H NMR ($CDCl_3$) δ 7.54 (1H, d, J = 5.3), 7.18 (1H, d, J = 7.18), 7.05 (1H, d, J = 5.4), 5.42 (1H, d, J = 8.9), 5.25 (1H, m), 5.02 (2H, m), 4.96-4.87 (1H, m), 4.65-4.42 (2H, m), 3.34-3.17 (1H, m), 2.97-2.93 (1H, m), 2.97 (3H, s), 2.87-2.78, 2.73-2.50, 2.38-2.32, 2.13-1.88, 1.69-1.60 (9H, 5m), 1.44 (9H, s).

[3*S*(1*S*,9*S*)] 5-(3-Chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoic acid (505e). A solution of **217** (0.33g, 0.51mmol) in dry dichloromethane (3ml) was cooled (ice/water) with protection from moisture. Trifluoroacetic acid (2ml) was added with stirring. The solution was kept at room temperature for 2h after removal of the cooling bath, then concentrated in vacuo. The residue was evaporated three times from dichloromethane, triturated with diethyl ether and filtered. The solid was purified by flash chromatography (silica gel, 0-6% methanol in dichloromethane) to give the product as a white glassy solid (0.296g, 98%): mp 110-122°C; $[\alpha]_D^{22}$ -163.5° (c 0.1, CH_3OH); IR (KBr) 3514-3337, 1726, 1664, 1513, 1420, 1245, 1152, 1134, 990; ^1H NMR (CD_3OD) δ 7.79 (1H, d, J = 5.2), 7.12 (1H, d, J = 5.2), 5.20 (1H, m), 5.02-4.72 (2H, m, masked by H_2O), 4.59-4.32 (3H, m), 3.48-3.29, 3.08-2.75, 2.50-2.41, 2.31-2.22, 2.08-1.89, 1.72-1.63 (11H, 6m), 2.95 (3H, s).



506a-c,g **507a-c,g**

compound	R^1
506a **507a**	PhC(O)-
506b **507b**	$MeS(O)_2$-
506c **507c**	MeOC(O)-
506g **507g**	$CH_3C(O)$-

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-diazo-4-oxopentanoate (506a). A solution of **212e** (321mg, 0.929mmol) and (3*S*) t-butyl 3-amino-5-diazo-4-oxopentanoate (198mg, 0.929mmol) in dichloromethane (3ml) was cooled to 0° and N,N-diisopropylethylamine (0.16ml, 1.86mmol) and [2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium tetrafluoroborate (328mg, 1.02mmol) were added. The solution was stirred overnight at room temperature, diluted with ethyl acetate and washed with 1M $NaHSO_4$ (x2), aqueous $NaHCO_3$ (x2), brine, dried over magnesium sulphate and evaporated. Chromatography on silica gel eluting with ethyl acetate gave **506a** (425mg, 85%) as a colourless foam: $[\alpha]_D^{23}$ -124.9° (c 0.2, CH_2Cl_2); IR (KBr) 3332, 2111, 1728, 1658, 1532, 1421, 1392, 1367, 1279, 1256, 1155; ^1H NMR ($CDCl_3$) δ 7.82 (2H, m), 7.49 (3H, m), 7.28 (1H, d, J = 9.3), 7.05 (1H, d, J = 7.3), 5.06 (1H, s), 5.18 (2H, m), 4.78 (1H, m), 4.62 (1H, m), 3.29 (1H, m), 3.08-2.79 (3H, m), 2.58 (1H, dd, J = 16.8, 5.6), 2.20-

1.85 (4H, m), 1.70 (1H, m), 1.45 (9H, s). MS (ES^+) 539.58 (M - 1, 97.9%) 529.59 (100).

[3*S*(1*S*,9*S*)] t-Butyl 5-diazo-3-[6,10-dioxo-(9-methanesulphonamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (506b), was prepared by a similar method as compound **506a**. 74% as yellow orange solid: mp. 75°C (decomp.); $[\alpha]_D^{20}$ -92.0° (c 0.036, CH_2Cl_2); IR (KBr) 3438, 2904, 2113, 1728, 1669, 1523, 1368, 1328, 1155; ^1H NMR ($CDCl_3$) δ 7.48 (1H, d, J = 8.1), 5.83-5.68 (1H, m,), 5.55-5.50 (1H, m), 5.43-5.14 (1H, m), 4.83-4.45 (3H, m), 3.40-3.19 (1H, m), 2.98 (3H, s), 2.92-2.30 (4H, m), 2.24-1.70 (6H, m), 1.43 (9H, s).

[3*S*(1*S*,9*S*)] t-Butyl 5-diazo-3-[6,10-dioxo-(9-methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (506c), was prepared by a similar method as compound **506a** to afford a pale yellow foam (405mg, 82%): $[\alpha]_D^{20}$ -144° (c 0.2, CH_2Cl_2); IR (KBr) 3339, 2978, 2958, 2112, 1728, 1674, 1530, 1459, 1415, 1367, 1274, 1252, 1154, 1063; ^1H NMR ($CDCl_3$) δ 7.23 (1H, d, J = 8.2), 5.51-5.31 (2H, m), 5.21-5.16 (1H, m), 4.77-4.55 (3H, m), 3.68 (3H, s), 3.35-3.18 (1H, m), 3.04-2.51 (4H, m), 2.40-2.30 (1H, m), 2.09-1.66 (5H, m), 1.45 (9H,s). MS (ES^+) 493.

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-diazo-4-oxopentanoate (506g), was prepared by a similar

method as compound **506a**. 81%: $[\alpha]_D^{28}$ -146.7° (c 0.4, CH_2Cl_2); IR (KBr) 3438, 2904, 2113, 1728, 1669, 1523, 1368, 1328, 1155; ^1H NMR ($CDCl_3$) δ 7.32 (1H, d), 6.43 (1H, d), 5.50 (1H, s), 5.22 (1H, m), 4.94 (1H, m), 4.77 (1H, m), 4.60 (1H, m), 3.24 (1H, m), 3.03-2.52 (4H, m), 2.36 (1H, m), 2.10-1.64 (5H, m), 2.02 (3H, s), 1.45 (9H, s). Anal. Calcd for $C_{21}H_{20}N_6O_7$: C, 52.69; H, 6.32; N, 17.05. Found: C, 52.51; H, 6.27; N, 17.36. MS (ES^+) 477(M^+ - 1, 100%).

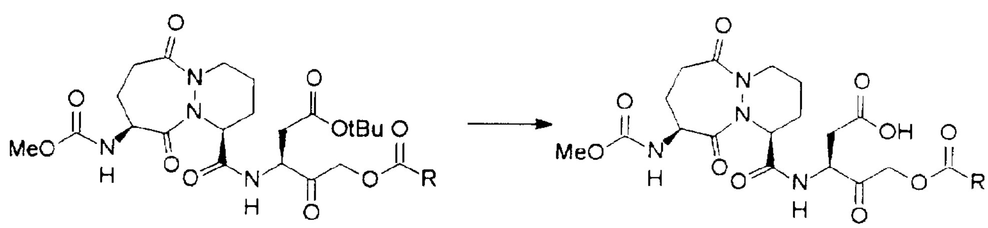
[3*S*(1*S*,9*S*)] t-Butyl 5-bromo-3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507a). **506a** (3.0g, 5.55mmol) in dry dichloromethane (40ml) was cooled to 0° and 30% hydrobromic acid in acetic acid (1.1ml, 5.55mmol) was added dropwise over 4min. The mixture was stirred at 0° for 9min and quenched with aqueous sodium bicarbonate. The product was extracted into ethyl acetate, washed with aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and evaporated to give 2.97g (92%) of a colourless foam: $[\alpha]_D^{23}$ -82.3° (c 0.23, CH_2Cl_2); IR (KBr) 3333, 1726, 1659, 1530, 1458, 1447, 1422, 1395, 1368, 1279, 1256, 1222, 1155, 728; ^1H NMR ($CDCl_3$) δ 7.81 (2H, m), 7.50 (3H, m), 7.11 (1H, d, J = 8.0), 7.01 (1H, d, J = 7.4), 5.20 (2H, m), 5.00 (1H, m), 4.06 (2H, s), 3.28 (1H, m), 3.20-2.70 (4H, m), 2.42 (1H, m), 2.10-1.85 (4H, m), 1.72 (1H, m), 1.44 (9H, s). Anal. Calcd for $C_{26}H_{33}N_4O_7Br \cdot 0.7H_2O$: C, 51.53; H, 5.72 N, 9.24. Found: C, 51.55; H, 5.52; N, 9.09. MS (ES^+) 595, 593 (M^+ + 1).

[3*S*(1*S*,9*S*)] t-Butyl 5-bromo-3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507b), was prepared by a similar method as compound **507a**. (68%) as an orange foam: $[\alpha]_D^{20}$ -135° (c 0.053, CH_2Cl_2); IR (KBr) 3429, 2944, 2935, 1723, 1670, 1458, 1408, 1327, 1225, 1154, 991; ^1H NMR ($CDCl_3$) δ 7.38 (1H, d, J = 8.2), 5.69 (1H, d, J = 9.3), 5,43-5.34 (1H, m), 5.07-4.97 (1H, m), 4.70-4.42 (2H, m), 4.12 (2H, s), 3.35-3.17 (1H, m), 3.10-2.69 (4H, m), 2.98 (3H, s), 2.43-2.33 (1H, m), 2.15-1.65 (5H, m), 1.43 (9H, s). Anal. Calcd for $C_{20}H_{31}BrN_4O_8S$: C, 42.33; H, 5.51; N, 9.87. Found: C, 42.69; H, 5.52; N, 9.97.

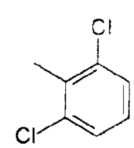
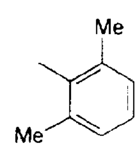
[3*S*(1*S*,9*S*)] t-Butyl 5-bromo-3-(6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507c), was prepared by a similar method as compound **507a** to afford a pale yellow foam (320mg, 78%): $[\alpha]_D^{20}$ -107° (c 0.2, CH_2Cl_2); IR (KBr) 3401, 2956, 1726, 1670, 1528, 1452, 1415, 1395, 1368, 1276, 1251, 1155, 1064; ^1H NMR ($CDCl_3$) δ 7.07 (1H, d, J = 7.6), 5.47 (1H, d, J = 8.1), 5.21-5.16 (1H, m), 5.03-4.94 (1H, m), 4.75-4.56 (2H, m), 4.06 (2H, s), 3.69 (3H, s), 3.31-3.13 (1H, m), 3.03-2.92 (2H, m), 2.81-2.58 (2H, m), 2.41-2.31 (1H, m), 2.10-1.66 (5H, m), 1.44 (9H, s).

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-acetylamino-6,10-dioxo—1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-bromo-4-oxopentanoate (507g), was prepared by a similar

method as compound **507a** to afford a pale yellow foam (84%): $[\alpha]_D^{22}$ -109.6° (c 0.1, CH_2Cl_2); IR (KBr) 3324, 1727, 1659, 1535, 1458, 1444, 1423, 1369, 1279, 1256, 1223, 1155; ^1H NMR ($CDCl_3$) δ 7.12 (1H, d, J = 7.8), 6.33 (1H, d, J = 7.5), 5.19 (1H, m,), 4.97 (2H, m), 4.58 (1H, m), 4.06 (2H, s), 3.20 (1H, m), 3.05-2.69 (4H, m), 2.35 (1H, m), 2.14-1.68 (5H, m), 2.03 (3H, s), 1.44 (9H, s). Anal. Calcd for $C_{21}H_{31}BrN_4O_7 \cdot 0.3H_2O$: C, 46.99; H, 5.93; N, 10.44. Found: C, 46.97; H, 5.90; N, 10.35.



508a, b **284, 285**

compound	R
508a **284**	
508b **285**	

[3*S*(1*S*,9*S*)] t-Butyl 5-(2,6-dichlorobenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoate (508a). To a solution of

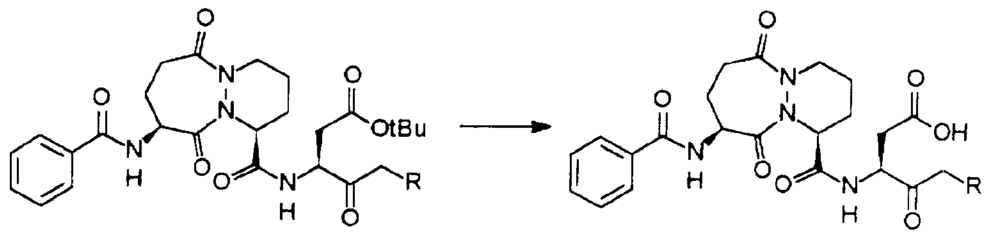
506c (547mg, 1mmol) in DMF (4ml) was added potassium fluoride (145mg, 2.5mmol, 2.5 equiv). After 10min stirring at room temperature, 2,6-dichlorobenzoic acid (229mg, 1.2mmol, 1.2 equiv) was added. After 3h reaction at room temperature, ethyl acetate (30ml) was added. The solution was washed with a saturated solution of sodium bicarbonate (30ml), brine, dried over $MgSO_4$ and concentrated in vacuo to afford 590mg (90%) of a pale yellow foam: $[\alpha]_D^{22}$ -85° (c 0.20, CH_2Cl_2); IR (KBr) 3400, 2956, 1737, 1675, 1528, 1434, 1414, 1368, 1344, 1272, 1197, 1152, 1061; ^1H NMR ($CDCl_3$) δ 7.36-7.33 (3H, m), 7.04 (1H, d, J = 8.0), 5.46 (1H, d, J = 7.8), 5.19-5.16 (1H, m), 5.08 (2H, AB), 4.97 - 4.55 (1H, m), 4.69-4.55 (2H, m), 3.68 (3H, s), 3.30-3.10 (1H, m), 3.01-2.50 (4H, m), 2.40-2.33 (1H, m), 2.15-1.60 (5H, m), 1.44 (9H, s). Anal. Calcd for $C_{28}H_{34}Cl_2N_4O_{10}$: C, 51.15; H, 5.21; N, 8.52. Found: C, 51.35; H, 5.32; N, 8.56.

[3*S*(1*S*,9*S*)] 5-(2,6-Dichlorobenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (284), was synthesized from **508a** via method used to prepare **505** from **504** which afforded 330mg (65%) of a white solid: mp. 115°C (decomp.); $[\alpha]_D^{20}$ -107° (c 0.2, CH_2Cl_2); IR (KBr) 3340, 2954, 1736, 1664, 1530, 1434, 1272, 1198, 1148, 1060; ^1H NMR (D_6-DMSO) δ 8.91 (1H, d, J = 7.2H), 7.67-7.63 (3H, m), 7.54 (1H, d, J = 8.0), 5.24 (2H, s), 5.20-5.15 (1H, m), 4.79-4.70 (1H, m), 4.46-4.37 (2H, m), 3.58 (3H, s), 3.33-3.20 (1H, m), 2.94-2.55 (4H, m), 2.30-1.60 (6H,

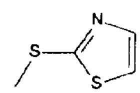
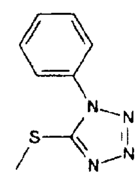
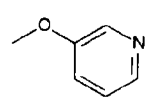
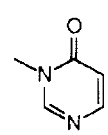
m). Anal. Calcd for $C_{24}H_{26}C_{12}N_4O_{10}\bullet H_2O$: C, 46.54; H, 4.56; N, 9.05. Found: C, 46.36; H, 4.14; N, 8.88.

[3*S*(1*S*,9*S*)] t-Butyl 5-(2,6-dimethylbenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (508b), was synthesized by a similar method as compound **508a** to afford a pale yellow foam (460mg, 82%): $[\alpha]_D^{22}$ -115° (c 0.20, CH_2Cl_2); IR (KBr) 3413, 2960, 1729, 1675, 1528, 1514, 1461, 1421, 1368, 1265, 1116, 1096; ^1H NMR ($CDCl_3$) δ 7.27-7.03 (4H, m), 5.48 (1H, d, J = 8.2), 5.20-5.14 (1H, m), 5.04 (2H, AB), 4.93-4.86 (1H, m), 4.80-4.56 (2H, m), 3.77 (3H, s), 3.32-3.15 (1H, m), 3.00-2.56 (4H, m), 2.37 (6H, s), 2.19-1.77 (5H, m), 1.45 (9H, s), 2.41-2.25 (1H, m). MS (ES^+) 617.

[3*S*(1*S*,9*S*)] 5-(2,6-Dimethylbenzoyloxy)3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (285), was synthesized by a similar method as compound **284** to afford a white solid (303mg, 78%): mp. 110°C (decomp.); $[\alpha]_D^{20}$ -128° (c 0.10, CH_2Cl_2); IR (KBr) 3339, 2958, 1731, 1666, 1529, 1420, 1266, 1248, 1115, 1070; ^1H NMR (D_6-DMSO) δ 8.90 (1H, d, J = 7.4), 7.54 (1H, d, J = 7.9), 7.36-7.28 (1H, m), 7.17-7.14 (2H, m), 5.19-5.15 (3H, m), 4.84-4.74 (1H, m), 4.45-4.37 (2H, m), 3.59 (3H, s), 3.45-3.25 (1H, m), 2.95-2.64 (4H, m), 2.35 (6H, s), 2.30-1.60 (6H, m). Anal. Calcd for $C_{26}H_{32}N_4O_{10}\bullet H_2O$: C, 53.98; H, 5.92; N, 9.68. Found: C, 53.50; H, 5.52; N, 9.49. MS (ES^+) 559.



509a-d 510a, 280, 283, 510d

compound	R
509a **510a**	
509b **280**	
509c **283**	
509d **510d**	

[3*S*(1*S*,9*S*)] **3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(2-mercaptothiazole)-4-oxopentanoic acid (510a).** A solution of **506a** (2.27g, 4.2mmol) in dry dichloromethane (50ml) was treated with 30% hydrobromic

acid in acetic acid (1.84ml, 9.2mmol, 2.2equiv) at 0°C, under nitrogen. After 10min stirring at 0°C the reaction was complete and a white solid crystallised in the medium. The solid was filtered and washed with ethylacetate and diethylether to afford 2.20g (100%) of [3*S*(1*S*,9*S*)] 5-bromo-3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoic acid which was used without further purification: ^{1}H NMR (D_6-DMSO) δ 8.87 (1H, d, J = 7.3), 8.63 (1H, d, J = 7.6), 7.91-7.87 (2H, m), 7.60-7.44 (3H, m), 6.92 (1H, bs), 5.14-5.09 (1H, m), 4.92-4.65 (2H, m), 4.43 (2H, AB), 4.41-4.35 (1H, m), 3.33-3.22 (1H, m), 2.98-2.90 (1H, m), 2.89-2.57 (2H, m), 2.35-2.15 (3H, m), 1.99-1.91 (2H, m), 1.75-1.60 (2H, m). A solution of the bromoketone (535mg, 1mmol) in dry DMF (10ml) was treated with potassium fluoride (150mg, 2.5mmol, 2.5 equiv), under nitrogen. After 5min stirring at room temperature, 2-mercaptothiazole (140mg, 1.2mmol, 1.2equiv) was added. After overnight reaction ethylacetate (150ml) was added and the organic solution was washed with brine, dried over magnesium sulphate and reduced in vacuo. The residue was crystallised in diethyl ether, filtered and purified on silica gel using a gradient of MeOH (0% to 5%) in dichloromethane. Evaporation afforded 344mg (60%) of a white solid: mp. 90-95°C (decomp.); $[\alpha]_D^{20}$ -82° (c 0.2, CH_2Cl_2); IR (KBr) 3328, 2941, 1745, 1659, 1535, 1422, 1276, 1255, 1223, 1072; ^{1}H NMR (D_6-DMSO) δ 8.92 (1H, d, J = 7.6), 8.68 (1H, d, J = 7.6), 7.98-7.90 (2H, m), 7.75-7.67 (1H, m), 7.64-7.50 (4H, m), 5.22-5.18 (1H, m), 4.95-4.74 (2H, m), 4.58-4.38 (3H, m), 3.52-3.19 (1H, m), 3.05-2.65 (4H, m), 2.40-1.50 (6H, m). Anal.

Calcd for $C_{25}H_{27}N_5O_4S_2{\bullet}H_2O$: C, 50.75; H, 4.94 N, 11.84. Found: C, 51.34; H, 4.70; N, 11.58. MS (ES^+) 572.

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1H-tetrazole-5-thio) pentanoate (509b). **507a** (100mg, 0.17mmol) in dry dimethylformamide (1.5ml) was treated with 1-phenyl-1H-tetrazole-5-thiol (33mg, 0.187mmol) and potassium fluoride (15mg, 0.34mmol). The mixture was stirred at room temperature for 2h, diluted with ethyl acetate, washed with aqueous sodium bicarbonate (x2), brine, dried ($MgSO_4$) and evaporated. The product was purified by flash chromatography on silica gel eluting with ethyl acetate to give 103mg (88%) as a colourless foam: $[\alpha]_D^{23}$ -92.2° (c 0.1, CH_2Cl_2); IR (KBr) 3334, 1726, 1660, 1528, 1501, 1417, 1394, 1368, 1279, 1253, 1155; ^{1}H NMR ($CDCl_3$) δ 7.82 (2H, m), 7.60-7.40 (8H, m), 7.39 (1H, d, J = 8.1), 7.05 (1H, d, J = 7.3), 5.26 (1H, m), 5.15 (1H, m), 4.99 (1H, m), 4.60 (2H, m), 4.30 (1H, d, J = 17.2H), 3.32 (1H, m), 3.10-2.75 (4H, m), 2.40 (1H, m), 2.24 (1H, m), 1.90 (3H, m), 1.75 (1H, m), 1.44 (9H, s). MS (ES^+) 691.47 (M^+ + 1).

[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio) pentanoic acid (280), was synthesized via method used to prepare **505** from **504**. **509b** (98mg, 0.142mmol) in dichloromethane (1ml) was cooled to 0° and trifluoroacetic acid (1ml) was added. The mixture was stirred at 0° for 15min and at

room temperature for 30min before evaporation under reduced pressure. The residue was triturated with dry toluene and evaporated. Chromatography on silica gel eluting with 10% methanol in dichloromethane gave a colourless glass which was crystallised from dichloromethane/diethyl ether to give 62mg (69%) of colourless solid: mp. 145°C (decomp.); $[\alpha]_D^{22}$ -80.9° (c 0.1, CH_2Cl_2); IR (KBr) 3400, 1727, 1658, 1530, 1501, 1460, 1445, 1416, 1280, 1254; ^{1}H NMR ($CDCl_3$) δ 8.00 (1H, m), 7.79 (2H, d, J = 6.7), 7.58-7.30 (9H, m), 5.25 (2H, m), 4.94 (1H, m), 4.53 (2H, m), 4.35 (1H, m), 3.35 (1H, m), 3.01 (3H, m), 2.73 (1H, m), 2.38 (1H, m), 1.98 (4H, m), 1.64 (1H, m). Anal. Calcd for $C_{29}H_{30}N_8O_7S{\cdot}0.2TFA$: C, 53.71; H, 4.63 N, 17.04. Found: C, 53.97; H, 4.92; N, 16.77. MS (ES$^+$) 633.55 (M$^+$ - 1).

[3*S*(1*S*,9*S*)] t-Butyl 3-[9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridyloxy)pentanoate (509c), was prepared by a similar method as compound **509b** to afford a colourless glass (34%): $[\alpha]_D^{22}$ -77.1° (c 0.25, CH_2Cl_2); IR (film) 3311, 1724, 1658, 1603, 1578, 1536, 1488, 1458, 1426, 1368, 1340, 1279, 1256, 1231, 1155, 707; ^{1}H NMR ($CDCl_3$) δ 8.29 (2H, m), 7.84 (2H, m), 7.48 (4H, m), 7.22 (3H, m), 5.20 (2H, m), 4.90 (2H, m), 4.58 (1H, m), 3.29 (1H, m), 3.20-2.70 (4H, m), 2.38 (2H, m), 1.96 (4H, m), 1.68 (1H, m), 1.42 (9H, s). MS (ES$^+$) 608.54 (M + 1).

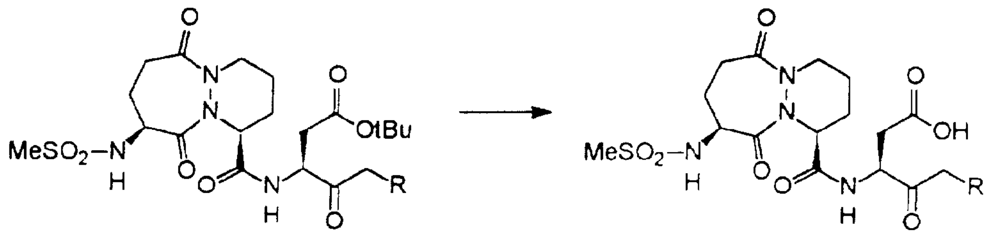
[3*S*(1*S*,9*S*)] 3-[9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-

(3-pyridyloxy)pentanoic acid (283), was prepared by a similar method as compound **280** to afford a colourless foam (100%): mp. ~125°C; $[\alpha]_D^{19}$ -84.1° (c 0.1, 20% MeOH/CH_2Cl_2); IR (KBr) 3401, 1736, 1663, 1538, 1489, 1459, 1425, 1281, 1258, 1200, 1134; ^{1}H NMR (CD_3OD/$CDCl_3$) δ 8.38 (2H, m), 7.84-7.40 (8H, m), 5.16 (4H, m), 4.80 (1H, m), 4.56 (1H, m), 3.50 (1H, m), 3.12 (2H, m), 2.82 (2H, m), 2.37 (1H, m), 2.10-1.65 (5H, m). Anal. Calcd for $C_{27}H_{29}N_5O_8 \cdot 0.4H_2O$: C, 51.77; H, 4.61; N, 10.41. Found: C, 52.19; H, 4.93; N, 9.99.

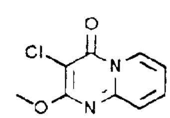
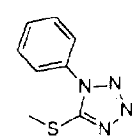
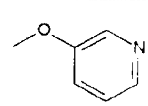
[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(phenycarbonylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-{2-[4(3H)-pyrimidone]}pentanoate (509d), was synthesized by a similar method as compound **509b** to afford a colourless solid (49.6mg, 82%): ^{1}H NMR ($CDCl_3$) δ 8.02 (1H, s), 7.95-7.86 (1H, m), 7.84-7.76 (2H, m), 7.62-7.35 (4H, m), 7.22-7.07 (1H, m), 6.43 (1H, d), 5.26-5.08 (2H, m), 5.03-4.72 (3H, m), 4.66-4.50 (1H, m), 3.43-3.19 (1H, m), 3.15-2.97 (1H, m), 2.86-2.72 (3H, m), 2.48-2.31 (1H, m), 2.18-1.60 (6H, m), 1.43 (9H, s).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(phenycarbonylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-{2-[4(3H)-pyrimidone]}pentanoic acid (510d), was synthesized by a similar method as compound **280** to afford a colourless solid (25.7mg, 57%): mp. 140-80°C; IR (KBr) 3391, 2945, 1733, 1664, 1530, 1422, 1363, 1277, 1259, 1204; ^{1}H NMR (CD_3OD) δ 8.23 (1H, s), 7.94

(1H, d), 7.87 (2H, d), 7.54-7.42 (3H, m), 6.48 (1H, d), 5.22-5.15 (1H, m), 4.57-4.46 (1H, m), 3.62-3.41 (1H, m), 3.22-3.13 (1H, m), 3.02-2.81 (2H, m), 2.70-1.80 (6H, m). Anal. Calcd for $C_{26}H_{28}N_6O_8 \cdot 1.5H_2O$: C, 54.30; H, 5.35; N, 14.61. Found: C, 54.14; H, 5.35; N, 13.04. MS (ES^+) 551 (M - 1, 100%). Accurate mass calculated for $C_{26}H_{29}N_6O_8$ (MH^+): 553.2047. Found: 553.2080.



504f-h → 505f, 280b, 283b

compound	R
504f 505f	
504g 280b	
504h 283b	

[3*S*(1*S*,9*S*)] 5-(3-Chloro-2-oxy-4H-pyrido[1,2-a]pyrimidin-4-one)-3-[6,10-dioxo-9-

(methylsulphonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (505f), was prepared by a similar method as compound **508a** using **507b** and 3-chloro-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one and directly followed by the hydrolysis of **504f** with trifluoroacetic to afford a tan powder (65mg, 30%): $[a]_D^{20}$ -128° (c 0.10, MeOH); IR (KBr) 3414, 2928, 1667, 1527, 2459, 1407, 1328, 1274, 1153, 1134; ^{1}H NMR (MeOD) δ 9.35 (1H, d, J = 6.6H), 8.34 (1H, t, J = 7.2H), 7.99-7.95 (1H, m), 7.76-7.69 (1H, m), 5.85-5.45 (3H, m), 5.30-5.21 (1H, m), 4.93-4.66 (2H, m), 3.81-3.65 (1H, m), 3.66 (3H, m), 3.45-2.52 (4H, m), 2.52-1.71 (6H, m). D.J. Hlasta et al., J. Med. Chem. 1995, 38, 4687-4692.

[3*S*(1*S*,9*S*)] t-Butyl 3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio)pentanoate (504g), was prepared by a similar method as compound **509b**, (83%) as a colourless foam: $[\alpha]_D^{23}$ -112.7° (c 0.2, CH_2Cl_2); IR (KBr) 3312, 1726, 1668, 1501, 1413, 1395, 1369, 1328, 1276, 1254, 1155; ^{1}H NMR ($CDCl_3$) δ 7.59 (5H, m), 7.48 (1H, d, J = 8.0), 5.68 (1H, d, J = 9.0), 5.37 (1H, m), 4.95 (1H, m), 4.62-4.31 (4H, m), 3.36 (1H, m), 2.98 (3H, s), 2.88 (4H, m), 2.66 (1H, m), 2.42 (2H, m), 1.98 (1H, m), 1.75 (1H, m), 1.43 (9H, s).

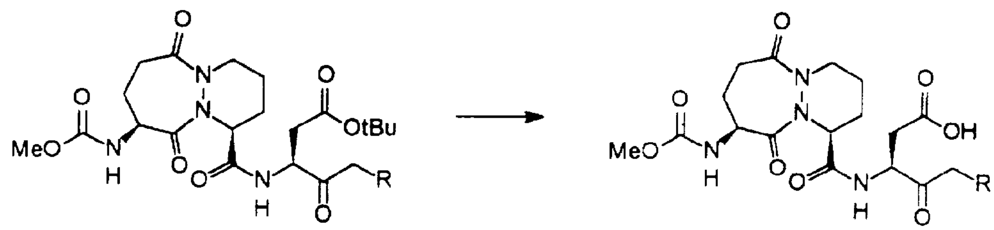
[3*S*(1S,9S)] 3-(6,10-Dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio)pentanoic acid (280b),

was prepared by a similar method as compound **280**, (100%) as a colourless foam: mp. 120-5°C; $[\alpha]_D^{25}$ -112.4° (c 0.1, CH_2Cl_2); IR (KBr) 3328, 1730, 1664, 1529, 1501, 1410, 1328, 1277, 1219, 1153, 1134, 991; ^1H NMR ($CDCl_3$) δ 8.07 (1H, d, J = 7.8), 7.58 (5H, s), 6.41 (1H, d, J = 9.5), 5.32 (1H, m), 5.04 (1H, m), 4.70 (1H, d, J = 17.5), 4.60 (3H, m), 3.50-2.9 (3H, m), 2.98 (3H, s), 2.45 (2H, m), 2.06 (4H, m), 1.68 (1H, m).

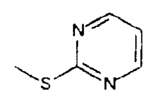
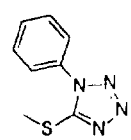
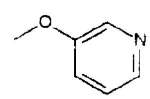
[3*S*(1*S*,9*S*)] t-Butyl 3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(3-pyridyloxy)pentanoate (504h), was prepared by a similar method as compound **509b** (24%) as a colourless foam: $[\alpha]_D^{23}$ -101.0° (c 0.2, CH_2Cl_2); IR (KBr) 3330, 1727, 1669, 1425, 1396, 1369, 1328, 1276, 1256, 1231, 1155, 1137, 991; ^1H NMR ($CDCl_3$) δ 8.28 (2H, br d, J = 9.4), 7.71 (1H, d, J = 7.9), 7.22 (2H, s), 6.03 (1H, d, J = 9.4), 5.36 (1H, m), 4.95 (2H, m), 4.52 (2H, m), 3.29 (1H, m), 3.07 (3H, s), 3.23-2.75 (3H, m), 2.66-2.35 (2H, m), 2.30-1.60 (5H, m), 1.42 (9H, s).

[3*S*(1*S*,9*S*)] 3-(6,10-Dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(3-pyridyloxy)pentanoic acid (283b), was prepared by a similar method as compound **280**, (100%) as a colourless foam: mp. 120-5°C ; $[\alpha]_D^{25}$ -85.2° (c 0.1, 10% CH_3OH/CH_2Cl_2); IR (KBr) 3337, 1738, 1667, 1560, 1457, 1424, 1326, 1317, 1278, 1258, 1200, 1189, 1150, 1133, 991; ^1H NMR ($CDCl_3/CD_3OD$) δ 8.35 (2H, m), 7.54 (2H, m),

5.32 (2H, m), 4.83 (2H, m), 4.45 (2H, m), 3.43-2.77 (4H, m), 2.97 (3H, s), 2.42 (2H, m), 2.05-1.72 (5H, m).



508c-e **511c, 280c, 283c**

compound	R
508c **511c**	
508d **280c**	
508e **283c**	

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(2-mercaptopyrimidine)-4-oxo-pentanoate (508c), was prepared by a similar method as compound **509b** to afford 544mg (97%) of a pale yellow foam: $[\alpha]_D^{20}$ -86° (c 0.19, CH_2Cl_2); IR (KBr) 3426, 2947, 1725, 1669, 1551, 1418,

1383, 1253, 1155, 1064; ^1H NMR ($CDCl_3$) δ 8.49 (2H, d, J = 4.8), 7.13 (1H, d, J = 7.9), 7.03-6.98 (1H, m), 5.47 (1H, d, J = 7.9), 5.23-5.19 (1H, m), 5.09-5.01 (1H, m), 4.84-4.51 (2H, m), 4.04 (2H, AB), 3.69 (3H, s), 3.38-3.19 (1H, m), 3.06-2.64 (4H, m), 2.40-1.76 (6H, m), 1.43 (9H, s). Anal. Calcd for $C_{25}H_{34}N_6O_8S$: C, 51.89; H, 5.92; N, 14.52. Found: C, 51.49; H, 6.04; N, 13.87. MS (ES^+) 579.

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methoxycarbonyl)-amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(2-mercaptopyrimidine)-4-oxopentanoic acid (511c), was prepared by a similar method as compound **280** to afford 370mg (79%) of a white powder: mp. 105°C (dec); $[\alpha]_D^{22}$ -94° (c 0.20, CH_2Cl_2); IR (KBr) 3316, 3057, 2957, 1724, 1664, 1252, 1416, 1384, 1254, 1189, 1063; ^1H NMR (D_6-DMSO) δ 8.85 (1H, d, J = 7.8), 8.62 (2H, d, J = 4.7), 7.53 (1H, d, J = 8.0), 7.28-7.23 (1H, m), 5.21-5.17 (1H, m), 4.87-4.79 (1H, m), 4.47-4.35 (2H, m), 4.23 (2H, AB), 3.58 (3H, s), 3.30-3.21 (1H, m), 2.95-2.50 (4H, m), 2.35-1.60 (6H, m). Anal. Calcd for $C_{21}H_{26}N_6O_8S \cdot H_2O$: C, 46.66; H, 5.22; N, 15.55. Found: C, 46.66; H, 5.13; N, 15.07. MS (ES^+) 523, (ES^+) 521.

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-[5-(1-phenyltetrazolyl)-thio]pentanoate (508d), was synthesized by a similar method as compound **509b** to afford a colourless solid (269mg, 87%): mp. 80-110°C; $[\alpha]_D^{23}$ -108° (c 0.60 CH_2Cl_2); IR (KBr) 3315, 2977, 1727,

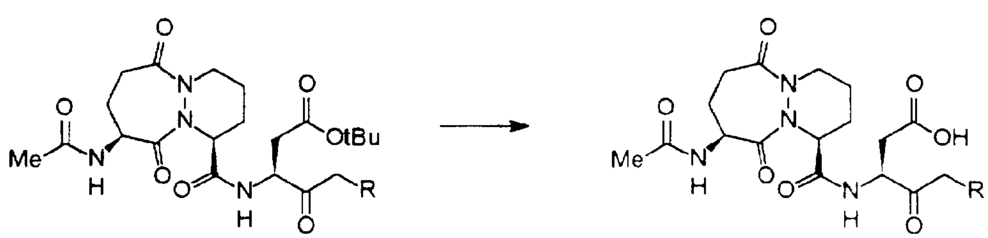
1688, 1527, 1501, 1458, 1418, 1368, 1279, 1250, 1155, 1064; ^{1}H NMR ($CDCl_3$) δ 7.70 (1H, d), 7.63-7.53 (5H, m), 5.84 (1H, d), 5.34-5.27 (1H, m), 5.05-4.92 (1H, m), 4.78-4.54 (3H, m), 4.38 (1H, d), 3.66 (3H, s), 3.37-3.19 (1H, m), 3.07-2.94 (1H, m), 2.91-2.82 (2H, m), 2.71-2.56 (1H, m), 2.40-2.30 (1H, m), 2.19-2.13 (1H, m), 2.08-1.68 (4H, m), 1.42 (9H, s). MS (ES^+) 667 (31%), 645 (M^+ + 1, 100), 589 (62).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-[5-(1-phenyltetrazolyl)-thio]pentanoic acid (280c), was synthesized by a similar method as compound **280** to afford a pale cream solid (203mg, 88%): mp. 105-130°C; $[\alpha]_D^{22}$ -235° (c 0.11 MeOH); IR (KBr) 3342, 2951, 1727, 1667, 1529, 1501, 1459, 1416, 1276, 1252, 1225, 1192, 1062; ^{1}H NMR (D_6-DMSO) δ 8.89 (1H, d), 7.69 (5H, s), 7.50 (1H, d), 5.18-5.11 (1H, m), 4.79-4.69 (1H, m), 4.57 (2H, s), 4.42-4.32 (1H, m), 3.54 (3H, s), 2.92-2.63 (3H, m), 2.21-1.82 (5H, m), 1.65-1.57 (1H, m). MS (ES^+) 587 (M - 1, 100%).

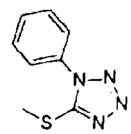
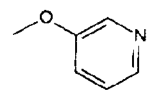
[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridinyloxy) pentanoate (508e), was synthesized by a similar method as compound **509b** to afford a pale orange solid (199mg, 25%): mp. 80-120°C; $[\alpha]_D^{23}$ -89° (c 0.51 CH_2Cl_2); IR (KBr) 3333, 2978, 1726, 1669, 1578, 1536, 1478, 1426, 1368, 1277, 1253, 1232, 1155, 1064; ^{1}H NMR ($CDCl_3$) δ 8.41-8.18 (2H, m), 7.81 (1H, d), 7.26-

7.20 (2H, s), 5.91 (1H, d), 5.24-5.16 (1H, m), 5.07-4.86 (3H, m), 4.81-4.51 (2H, m), 3.67 (3H, s), 3.34-3.16 (1H, m), 3.10-2.81 (3H, m), 2.72-2.54 (1H, m), 2.41-2.31 (1H, m), 2.07-1.62 (5H, m), 1.47 (9H s). MS (ES^+) 562 (M^+ + 1, 100%), 506 (38).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridinyloxy)pentanoic acid (283c), was synthesized by a similar method as compound **280** to afford an off-white powder (167mg, 98%): mp. 90-105°C; $[\alpha]_D^{22}$ -106° (c 0.11 MeOH); IR (KBr) 3325, 3070, 2956, 1669, 1544, 1423, 1256, 1199, 1133, 1062; ^{1}H NMR (D_6-DMSO) δ 8.95 (1H, d), 8.45-8.20 (2H, m), 7.53-7.45 (3H, m), 5.19-5.08 (3H, m), 4.70-4.62 (1H, m), 4.41-4.30 (2H, m), 3.53 (3H, s), 2.92-2.68 (3H, m), 2.22-2.06 (2H, m), 1.95-1.82 (2H, m), 1.63-1.53 (1H, m). MS (ES^+) 506 (M^+ + 1, 100%).



512a, 512b 280d, 283d

compound	R
512a **280d**	
512b **283d**	

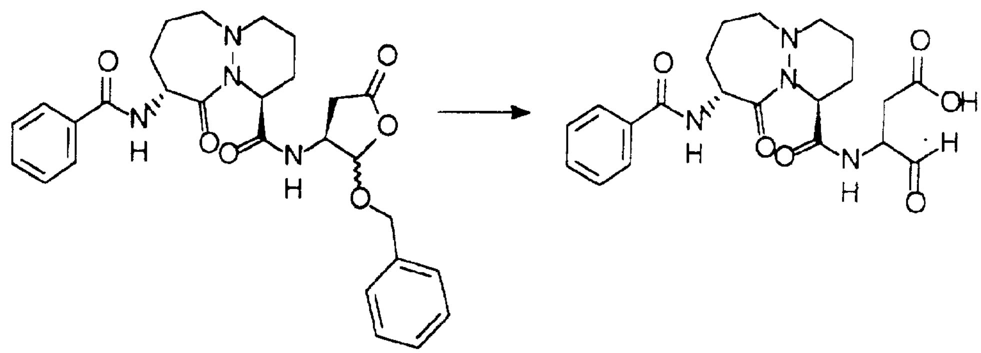
[3*S*(1*S*,9*S*)] t-Butyl 3-(9-acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1H-tetrazole-5-thio)pentanoate (512a), was prepared by a similar method as compound **509b**, to afford (83%) as a colourless foam: $[\alpha]_D^{23}$ -129.6° (c 0.1, CH_2Cl_2); IR (KBr) 3323, 1726, 1664, 1531, 1501, 1444, 1415, 1394, 1369, 1279, 1254, 1156; ^{1}H NMR ($CDCl_3$) δ 7.59 (5H, s), 7.37 (1H, d, J = 7.9), 6.38 (1H, d, J = 7.4), 5.27 (1H, m), 4.98 (2H, m), 4.58 (2H, d + m), 4.28 (1H, d, J = 17.2), 3.28 (1H, m), 3.10-2.65 (4H, m), 2.31 (2H, m), 2.03 (3H, s), 2.10-1.72 (4H, m), 1.48 (9H, s).

[3*S*(1*S*,9*S*)] 3-(9-Acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1H-tetrazole-5-thio)pentanoic acid (280d), was prepared by a similar method as compound **280**, to afford (77%) as a colourless foam: $[\alpha]_D^{22}$ -93.3° (c 0.1, CH_2Cl_2); IR (KBr) 3316,

1728, 1659, 1531, 1501, 1415, 1341, 1278, 1253, 1222, 1185; ^{1}H NMR ($CDCl_3$) δ 8.05 (1H, d, J = 7.9), 7.57 (5H, br s), 5.30 (1H, m), 5.01 (2H, m), 4.70-4.10 (4H, m), 3.40-2.85 (4H, m), 2.62 (1H, m), 2.33 (1H, m), 2.27-1.65 (5H, m), 2.01 (3H, s).

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(3-pyridyloxy)pentanoate (512b), was prepared by a similar method as compound **509b**, to afford (9%) as a colourless foam: IR (KBr) 3333, 1727, 1661, 1542, 1427, 1369, 1279, 1257, 1232, 1156; ^{1}H NMR ($CDCl_3$) δ 8.30 (2H, m), 7.20 (3H, m), 6.45 (1H, d, J = 7.4), 5.17 (1H, m), 4.91 (3H, m), 4.55 (1H, m), 3.27 (1H, m), 3.14-2.70 (4H, m), 2.41 (1H, m), 2.04 (3H, s), 2.10-1.65 (6H, m), 1.44 (9H, s).

[3*S*(1*S*,9*S*)] 3-(9-Acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(3-pyridyloxy)pentanoic acid (283d), was prepared by a similar method as compound **280**. (100%) as a colourless foam: $[\alpha]_D^{22}$ -106.0° (c 0.2, 10% CH_3OH/CH_2Cl_2); IR (KBr) 3312, 1735, 1664, 1549, 1426, 1279, 1258, 1200, 1135; ^{1}H NMR ($CDCl_3$) δ 8.27 (2H, m), 7.46 (2H, m), 5.09 (1H, m), 4.79 (3H, m), 4.47 (1H, m), 3.40 (1H, m), 3.30-2.70 (3H, m), 2.54 (1H, m), 2.30 (1H, m), 1.98 (3H, s), 2.05-1.65 (4H, m).



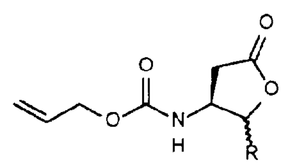
245b 246b

[1*S*,9*R*(2*RS*,3*S*)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-1,2,3,4,7,8,9,10-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (245b), was prepared from (1*S*,9*R*) 9-Benzoylamino-1,2,3,4,7,8,9,10-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid by the method described for **245** to afford 416mg (85%) of a colourless foam (~1:1 mixture of diastereoisomers): IR (KBr) 3392, 3302, 2942, 1792, 1642, 1529, 1520, 1454, 1119; ^{1}H NMR ($CDCl_3$) δ 7.79 (2H, m), 7.51-7.09 (10H, m), 5.52 (0.5H, d, J = 5.3), 5.51 (0.5H, s), 5.36 (1H, m), 4.84 (1H, m), 4.74-4.59 (1.5H, m), 4.51 (1H, m), 4.38 (0.5H, m), 3.22-2.83 (5H, m), 2.51 (1H, m), 2.25 (2H, m), 2.01-1.46 (6H, m). Anal. Calcd for $C_{28}H_{32}N_4O_6$•$0.75H_2O$: C, 62.97; H, 6.32; N, 10.49. Found: C, 63.10; H, 6.16; N, 10.21. MS (ES$^+$) 521 (M + 1, 100%).

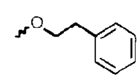
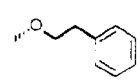
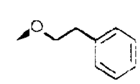
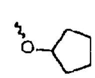
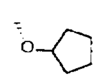
[3*S*(1*S*,9*R*)] 3-(9-Benzoylamino-1,2,3,4,7,8,9,10-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (246b), was prepared from **245b** by the method described for **246** to afford

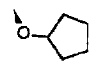
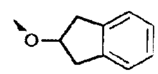
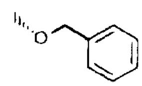
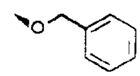
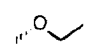
104mg (33%) of a white powder: mp. 115-119°C; $[\alpha]_D^{24}$ -19.8° (c 0.2 MeOH); IR (KBr) 3293, 2944, 1786, 1639, 1578, 1537, 1489, 1450, 1329, 1162, 1124; ^1H NMR (CD_3OD) δ 7.85 (2H, d, J = 7.0), 7.49 (3H, m), 5.49 (1H, m), 4.55 (1H, m), 4.30 (2H, m), 3.40 (1H, m), 3.19-2.89 (3H, m), 2.63 (2H, m), 2.16-1.81 (5H, m), 1.60 (3H, m). Anal. Calcd for $C_{21}H_{26}N_4O_6 \cdot H_2O$: C, 56.24; H, 6.29; N, 12.49. Found: C, 56.54; H, 6.05; N, 12.29. MS (ES^+) 429 (M - 1, 100%).

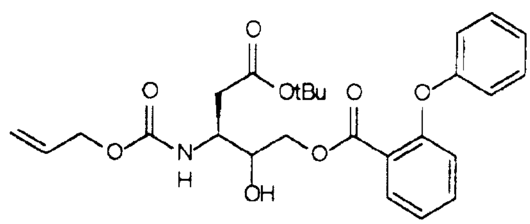
Compounds **513a-j** were prepared as described below.



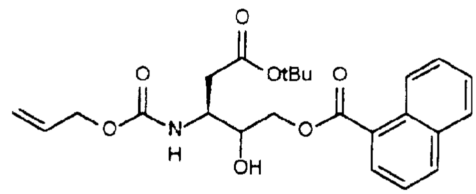
513a-f

compound	R
513a	
513a-1	
513a-2	
513b	
513b-1	

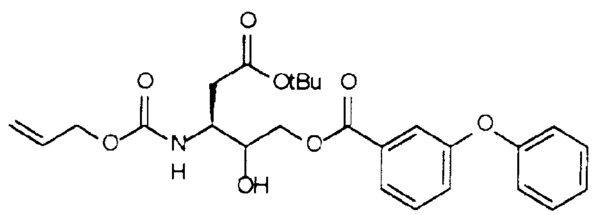
513b-2	
513c	
513d	
513e	
513f	
513f-1	
513f-2	



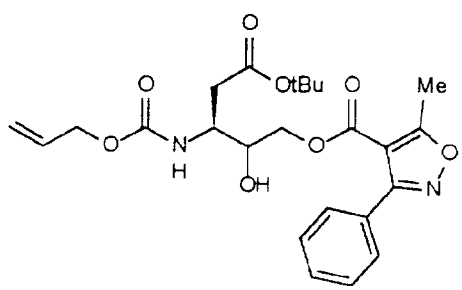
513g



513h



513i



513j

(2*RS*,3*S*) 3-(Allyloxycarbonyl)amino-2-(2-phenethyloxy)-5-oxotetrahydrofuran (513a), was prepared by a similar method as compound **513d/e** to afford a mixture of diastereoisomers (670mg, 50%) as an oil: IR (KBr) 3331, 2946, 1790, 1723, 1713, 1531, 1329, 1257, 1164, 1120, 1060, 977, 937, 701; ^{1}H NMR ($CDCl_3$) δ 7.36-7.18 (5H, m), 5.99-5.83 (1H, m), 5.41-5.34 (2H, m), 5.28-5.18 (2H,

m), 4.59-4.56 (2H, m), 4.32-3.96 (2H, m), 3.85-3.73 (1H, m), 3.02-2.76 (3H, m), 2.49-2.34 (1H, m).

(2*RS*,3*S*) 3-(Allyloxycarbonyl)amino-2-cyclopentyloxy-5-oxotetrahydrofuran (513b), was prepared as **513d/e** to afford 8g (51%) of a mixture of diastereoisomers as a clear oil: $[\alpha]_D^{20}$ -13° (c 0.25, CH_2Cl_2); IR (KBr) 3325, 2959, 2875, 1790, 1723, 1535, 1420, 1328, 1257, 1120, 1049, 973, 937; ^1H NMR ($CDCl_3$) δ 6.02-5.80 (1H, m), 5.53-5.46 (2H, m), 5.37-5.21 (2H, m), 4.58 (2H, d, J = 5.5), 4.50-4.46 (0.5H, m), 4.34-4.25 (1H, m), 4.19-4.12 (0.5H, m), 3.06-2.77 (1H, m), 2.53-2.35 (1H, m), 1.85-1.50 (8H, m). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 56.62; H, 7.22; N, 4.95. MS (ES^+) 270.

(2*R*,3*S*) 3-Allyloxycarbonylamino-2-(indan-2-yloxy)-5-oxotetrahydrofuran (513c), was synthesized by a similar method as compound **513d/e** to afford a single isomer (20%) as a pale yellow oil: $[\alpha]_D^{24}$ -63.1° (c 0.2, CH_2Cl_2); IR (film) 3338, 2948, 1791, 1723, 1529, 1421, 1330, 1253, 1122, 984, 929, 746; ^1H NMR ($CDCl_3$) δ 7.20 (4H, m), 5.87 (1H, m), 5.61 (1H, d, J = 5.4), 5.33-5.10 (2H, m), 4.70 (1H, m), 4.56 (3H, m), 3.33-3.19 (2H, m), 3.10-2.94 (2H, m), 2.81 (1H, dd, J = 8.3, 17.3), 2.43 (1H, dd, J = 10.5, 17.3).

(2*R*,3*S*) 3-Allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydro-furan (513d) and (2*S*,3*S*) 3-Allyloxycarbonylamino-2-benzyloxy-5-oxo-tetrahydrofuran (513d/e), were prepared [via method described by Chapman Biorg. & Med. Chem. Lett., 2, pp. 615-618

(1992)]. Following work-up by extraction with ethylacetate and washing with $NaHCO_3$, the product was dried ($MgSO_4$), filtered and evaporated to yield an oil which contained product and benzyl alcohol. Hexane (200ml) (200ml hexane for every 56g of AllocAsp(CO_2tBu)CH_2OH used) was added and the mixture stirred and cooled overnight. This afforded an oily solid. The liquors were decanted and retained for chromatography. The oily residue was dissolved in ethyl acetate and evaporated to afford an oil which was crystallised from 10% ethyl acetate in hexane (~500ml). The solid was filtered to afford **513d** (12.2g, 19%): mp. 108-110°C; $[\alpha]_D^{24}$ +75.72° (c 0.25, CH_2Cl_2); IR (KBr)3361, 1778, 1720, 1517, 1262, 1236, 1222, 1135, 1121, 944, 930, 760; ^{1}H NMR ($CDCl_3$) δ 7.38 (5H, m), 5.90 (1H, m), 5.50 (1H, s), 5.37 (0.5H, m), 5.26 (2.5H, m), 4.87 (1H, ABq), 4.63 (3H, m), 4.31 (1H, m), 3.07 (1H, dd), 2.46 (1H, dd). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.85; H, 5.89; N, 4.80.

The liquors were combined and evaporated to yield an oil (~200g) containing benzyl alcohol. Hexane/ethyl acetate (9:1, 100ml) was added and the product purified by chromatography eluting with 10% ethyl acetate in hexane to remove the excess benzyl alcohol, and then dichloromethane/hexane (1:1 containing 10% ethyl acetate). This afforded **513e** containing some **513d** (20.5g, 32%): mp. 45-48°C; $[\alpha]_D^{24}$ -71.26° (c 0.25, CH_2Cl_2); IR (KBr) 3332, 1804, 1691, 1536, 1279, 1252, 1125,976. ^{1}H NMR ($CDCl_3$) δ 7.38 (5H, m), 5.91 (1H, m), 5.54 (1H, d, J = 5.2), 5.38 (3H, m); 4.90 (1H, ABq); 4.60 (4H, m), 2.86 (1H, dd); 2.52 (1H,

dd). Anal. Calcd for $C_{15}H_{17}NO_5 \cdot 0.1H_2O$ C, 61.47; H, 5.91; N, 4.78. Found: C, 61.42; H, 5.88; N, 4.81.

(2*RS*,3*R*) 3-(Allyloxycarbonylamino)-2-ethoxy-5-oxotetrahydrofuran (513f), was synthesized by a similar method as **513d/e** to afford a colourless oil (152mg, 79%): IR (film) 3334, 2983, 2941, 1783, 1727, 1713, 1547, 1529, 1422, 1378, 1331, 1313, 1164, 1122, 1060, 938; ^{1}H NMR ($CDCl_3$) δ 6.09-5.82 (2H, m), 5.50-5.18 (3H, m), 4.64-4.54 (2H, m), 4.27-4.16 (1H, m), 3.95-3.78 (1H, m), 3.73-3.56 (1H, m), 3.05-2.77 (1H, m), 2.56-2.37 (1H, m), 1.35-1.17 (4H, m). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.16; H, 6.62; N, 5.99. MS (ES^+) 229 (M^+ + 1, 100%).

(3*S*,4*RS*) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(2-phenoxybenzoyloxy)pentanoate (513g). 4-Dimethylamino-pyridine (76.0mg, 622mmol) was added to a solution of 2-phenoxybenzoyl chloride (579mg, 2.49mmol) and **517** (600mg, 2.07mmol) in pyridine (10ml). The mixture was stirred at room temperature for 18h before adding brine (25ml) and extracting with ethyl acetate (30ml, 20ml). The combined organic extracts were washed with 1M hydrochloric acid (3 x 25ml), saturated aqueous sodium hydrogen carbonate (2 x 25ml) and brine (25ml), dried ($MgSO_4$) and concentrated. The pale orange oil was purified by flash column chromatography (1-10% acetone in dichloromethane) to afford 447mg (44%) of colourless oil: IR (film) 3375, 2980, 1721, 1712, 1602, 1579, 1514, 1484, 1451, 1368, 1294, 1250, 1234, 1161, 1137, 1081, 754; ^{1}H NMR ($CDCl_3$) δ 7.98-7.93 (1H, m), 7.50-7.41 (1H, m), 7.35-7.25 (2H, m), 7.22-7.03 (3H, m), 6.95 (3H, d), 5.95-5.76 (1H, m), 5.57

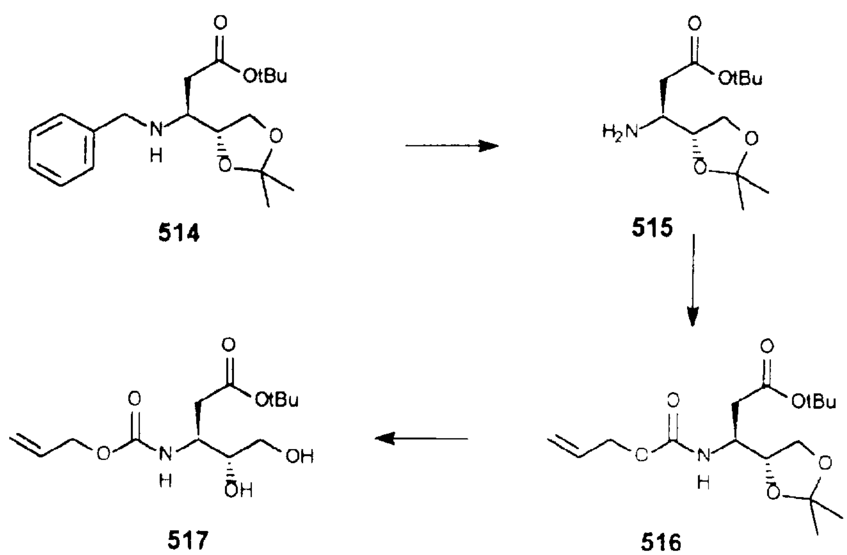
(1H, d), 5.30-5.13 (2H, m), 4.51 (2H, d), 4.25 (2H, d), 4.18-4.04 (1H, m), 3.88 (1H, m), 3.50 (1H, m), 2.51 (2H, m), 1.41 (9H, s). MS (ES^+) 508 (57%), 503 (76), 486 (M^+ + 1, 45), 468 (27), 412 (100). Accurate mass calculated for $C_{26}H_{32}NO_8$ (MH^+): 486.2128. Found: 486.2158.

(3*S*,4*R*) t-Butyl (N-allyloxycarbonyl)-3-amino-4-hydroxy-5-(1-naphthoyloxy)pentanoate (513h), was prepared from (3*S*,4*R*) t-butyl (N-allyloxycarbonyl)-3-amino-4,5-dihydroxypentanoate by the method described for **513g** to afford 562mg (85%) of a colourless oil: IR(film) 3418, 2980, 1722, 1711, 1512, 1368, 1278, 1245, 1198, 1157, 1139; ^{1}H NMR ($CDCl_3$) δ 8.90 (1H, d, J = 8.6), 8.21 (1H, dd, J = 1.2, 7.3), 8.04 (1H, d, J = 8.2), 7.89 (1H, dd, J = 1.5, 7.9), 7.67-7.46 (3H, m), 5.88 (1H, m), 5.49 (1H, d, J = 9.0), 5.35-5.18 (2H, m), 4.57-4.46 (4H, m), 4.19 (2H, m), 2.67 (2H, m), 1.40 (9H, s). Anal. Calcd for $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.74; H, 6.56; N, 3.09. M.S. (ES^+) 466 (M+Na, 100%), 444 (M+1, 39), 388 (44).

(3*S*,4*RS*) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(3-henoxybenzoyloxy)pentanoate (513i), was synthesized by a similar method as compound **513g** to afford a colourless oil (569mg, 85%): IR (film) 3400, 1723, 1712, 1584, 1528, 1489, 1443, 1367, 1276, 1232, 1190, 1161, 1098, 1074, 995, 755; ^{1}H NMR ($CDCl_3$) δ 8.65-8.59 (1H, d), 7.84-7.66 (2H, m), 7.45-711 (5H, m), 7.05-6.97 (2H, m), 6.00-5.78 (1H, m), 5.54-5.14 (2H, m), 4.62-4.52 (2H, m), 4.42-4.32 (2H, m), 4.08-4.22 (2H, m), 2.78-2.47 (2H, m), 1.44 (9H, s). MS (ES^+) 508 (100%),

486 (M^+ + 1, 33. Accurate mass calculated for $C_{26}H_{32}NO_8$ (MH^+): 486.2128. Found: 486.2121.

(3*S*,4*RS*) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(5-methyl-3-phenylisoxazoloyloxy)pentanoate (513j), was synthesized by a similar method as compound **513g** to afford a pale orange oil (905mg, 91%): IR (film) 3418, 3383, 2980, 1722, 1711, 1601, 1517, 1450, 1424, 1368, 1308, 1252, 1154, 1100, 994, 767, 698; ^1H NMR ($CDCl_3$) δ 7.62-7.55 (2H, m), 7.51-7.42 (3H, m), 5.98-5.76 (1H, m), 5.33-5.18 (2H, m), 4.53 (2H, d), 4.18 (2H, d), 3.91 (1H, m), 3.80 (1H, m), 2.76 (3H, s), 2.50 (2H, m), 1.43 (9H, s). Anal. Calcd for $C_{24}H_{30}N_2O_8 \cdot 0.5H_2O$: C, 59.62; H, 6.46; N, 5.79. Found: C, 59.46; H, 6.24; N, 5.72. MS (ES^+) 497 (100%), 475 (M^+ + 1, 15), 419 (48).



(3*S*,4*R*) t-Butyl 3-benzylamino-4,5-(dimethylmethylenedioxy)-pentanoate (514), was prepared by the method described in H. Matsunaga, et al.

Tetrahedron Letters 24, pp. 3009-3012 (1983) as a pure diastereomer (60%) as an oil: $[\alpha]_D^{23}$ -36.9° (c 0.5, dichloromethane); IR (film) 2982, 2934, 1726, 1455, 1369, 1257, 1214, 1157, 1068; ^{1}H NMR ($CDCl_3$) δ 7.31 (5H, m), 4.10 (1H, q, J = 6.0), 4.05-3.75 (4H, m), 3.10 (1H, q, J = 6.0), 2.40 (2H, m), 1.42 (9H, s), 1.40 (3H, s), 1.34 (3H, s).

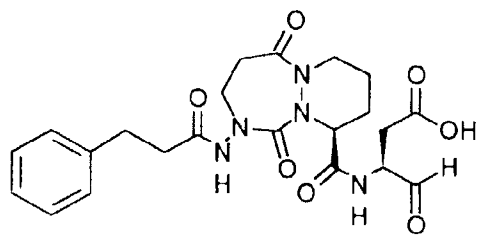
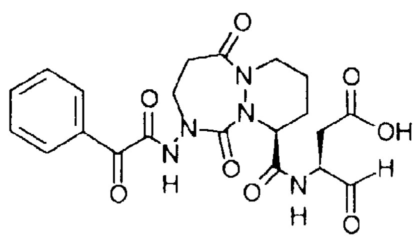
(3*S*,4*R*) t-Butyl 3-(allyloxycarbonylamino)-4,5-(dimethylmethylenedioxy)pentanoate (516). **514** (3.02g, 9.00mmol) and 10% palladium on carbon (300mg) in ethanol (30ml) were stirred under hydrogen for 2h. The suspension was filtered through celite and a 0.45mm membrane and the filtrate concentrated to give a colourless oil **515** (2.106g, 95%) which was used without purification. The oil (1.93g, 7.88mmol) was dissolved in water (10ml) and 1,4-dioxan and sodium hydrogen carbonate added (695mg, 8.27mmol). The mixture was cooled to 0°C and allyl chloroformate (1.04g, 919ml, 8.66mmol) added dropwise. After 3h the mixture was extracted with ether (2 x 50ml). The combined ether extracts were washed with water (2 x 25ml) and brine (25ml), dried ($MgSO_4$) and concentrated to give a colourless oil. Flash column chromatography (10-35% ethylacetate in hexane) afforded a colourless solid (2.69g, 95%): mp. 64-5°C; $[\alpha]_D^{23}$ -21° (c 1.00, CH_2Cl_2); IR (KBr) 3329, 1735, 1702; ^{1}H NMR ($CDCl_3$) δ 6.00-5.82 (1H, m), 5.36-5.14 (2H, m), 542 (1H, s), 4.56 (1H, d), 4.40-4.08 (2H, m), 4.03 (1H, m) 3.70 (1H, m), 2.52 (2H, m), 1.44 (12H, 2 x s), 1.33 (3H, s); Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found : C, 58.12; H, 8.16; N, 4.19; MS (+FAB) 320 (M^++1, 41%), 274 (70), 216 (100).

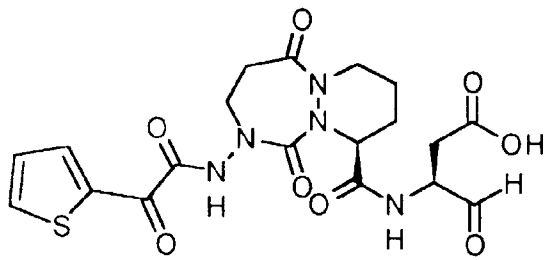
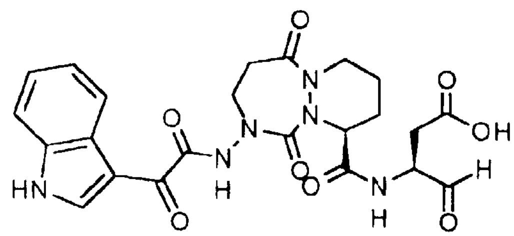
(3*S*,4*R*) t-Butyl 3-(allyloxycarbonylamino)4,5-dihydroxy pentanoate (517). A solution **516** (2.44g, 7.41mmol) in 80% aqueous acetic acid (25ml) was stirred at room temperature for 24h then concentrated and azeotroped with toluene (2 x 25ml). The residue was treated with brine (25ml) and extracted with ethylacetate (2 x 25ml). The organic fractions were dried ($MgSO_4$) and concentrated to afford a colourless oil. Flash chromatography (20-80% ethyl acetate in dichloromethane) gave a colourless solid (1.99g, 90%): mp. 74-5°C; $[\alpha]_D^{25}$ -1.3° (c 1.0, CH_2Cl_2); IR (KBr) 1723, 1691; ^1H NMR ($CDCl_3$) δ 6.02-5.78 (2H, m), 5.35-5.16 (2H, m), 4.55 (2H, d), 4.16-4.04 (2H, m), 2.76 (2H, s), 3.56 (2H, m), 2.56 (2H, m), 1.43 (9H, s); Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84. Found : C, 53.79; H, 7.88; N, 4.81; MS(+FAB) 290 (M^++1, 44%), 234 (100).

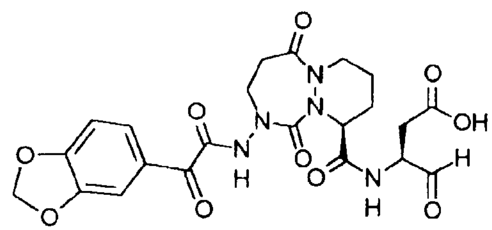
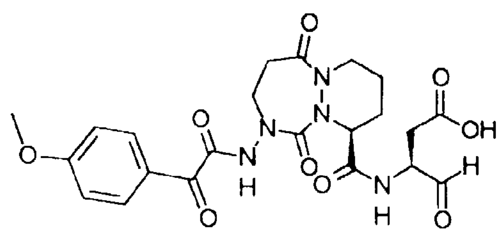
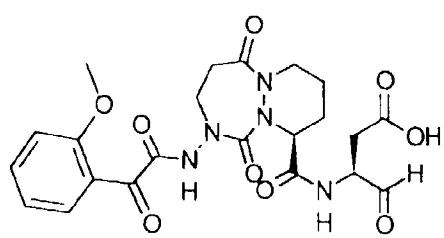
<u>Example 30</u>

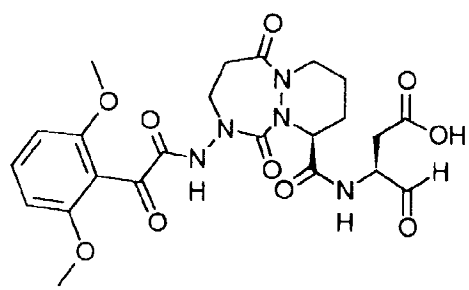
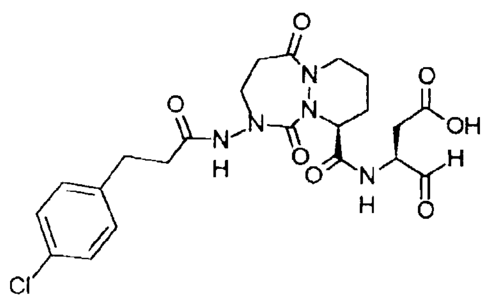
Compounds **1105-1125** were prepared as follows. Physical data for these compounds is listed in Table 24.

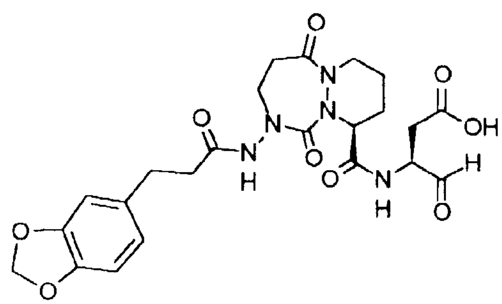
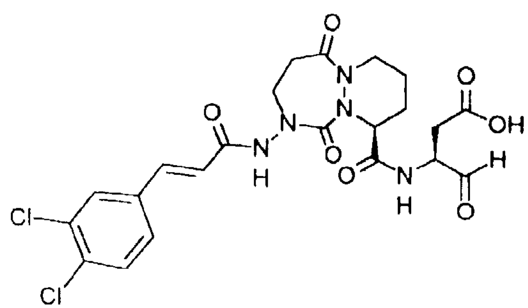
Table 24

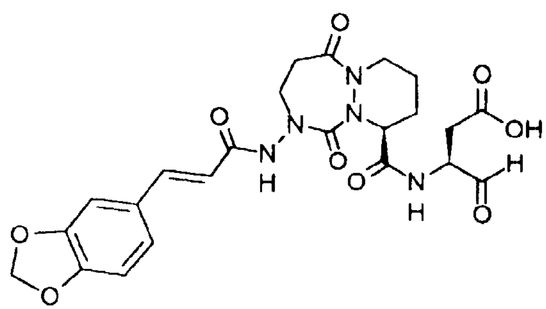
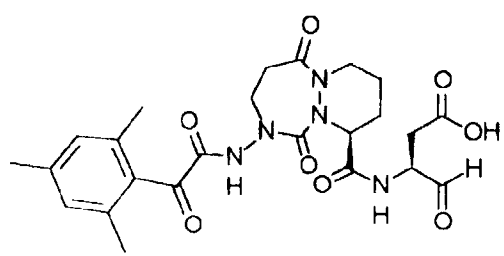
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1105		C22H27N5O7	473.49	12.769 (1) 99%	496.9
1106		C21H23N5O8	473.45	12.137 (1) 99%	496.9

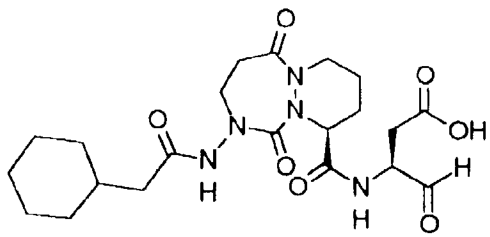
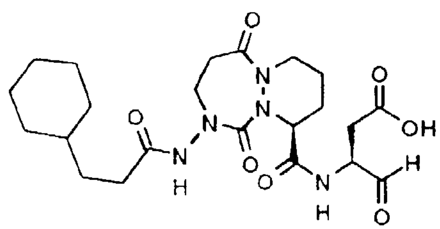
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1107		C19H21N5O8S	479.47	11.272 (1) 97%	502.9
1108		C23H24N6O8	512.48	13.699 (1) 97%	536.4

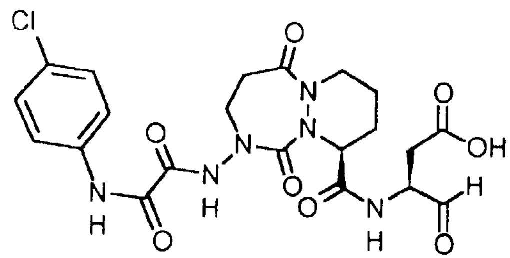
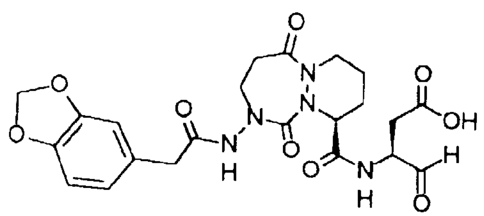
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1109		C22H23N5O10	517.46	12.341 (1) 92%	541.2
1110		C22H25N5O9	503.47	12.991 (1) 96%	527.9
1111		C22H25N5O9	503.47	10.951 (1) 99%	526.7

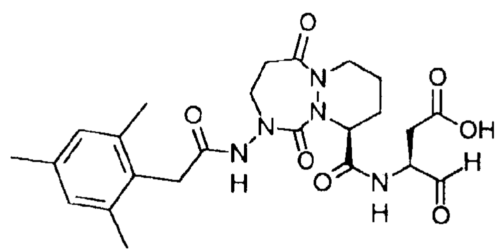
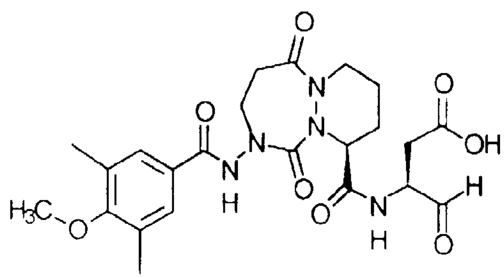
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1112		C23H27N5O10	533.50	11.377 (1) 98%	557.2
1113		C22H26ClN5O7	507.93	16.317 (1) 98%	531.5

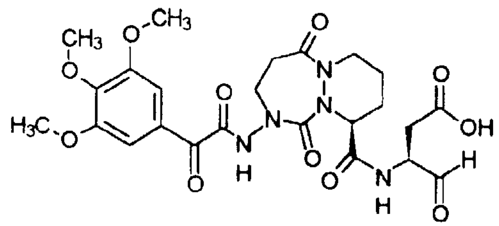
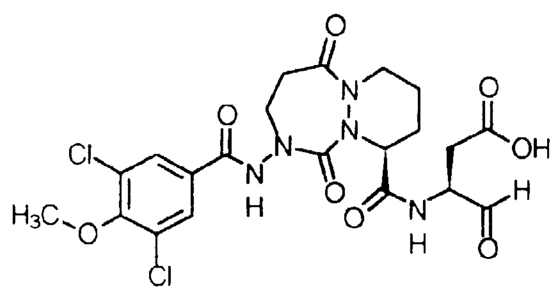
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1114		C23H27N5O9	517.50	12.902 (1) 99%	542.4
1115		C22H23Cl2N5O7	540.36	12.529 (2) 97%	563.4

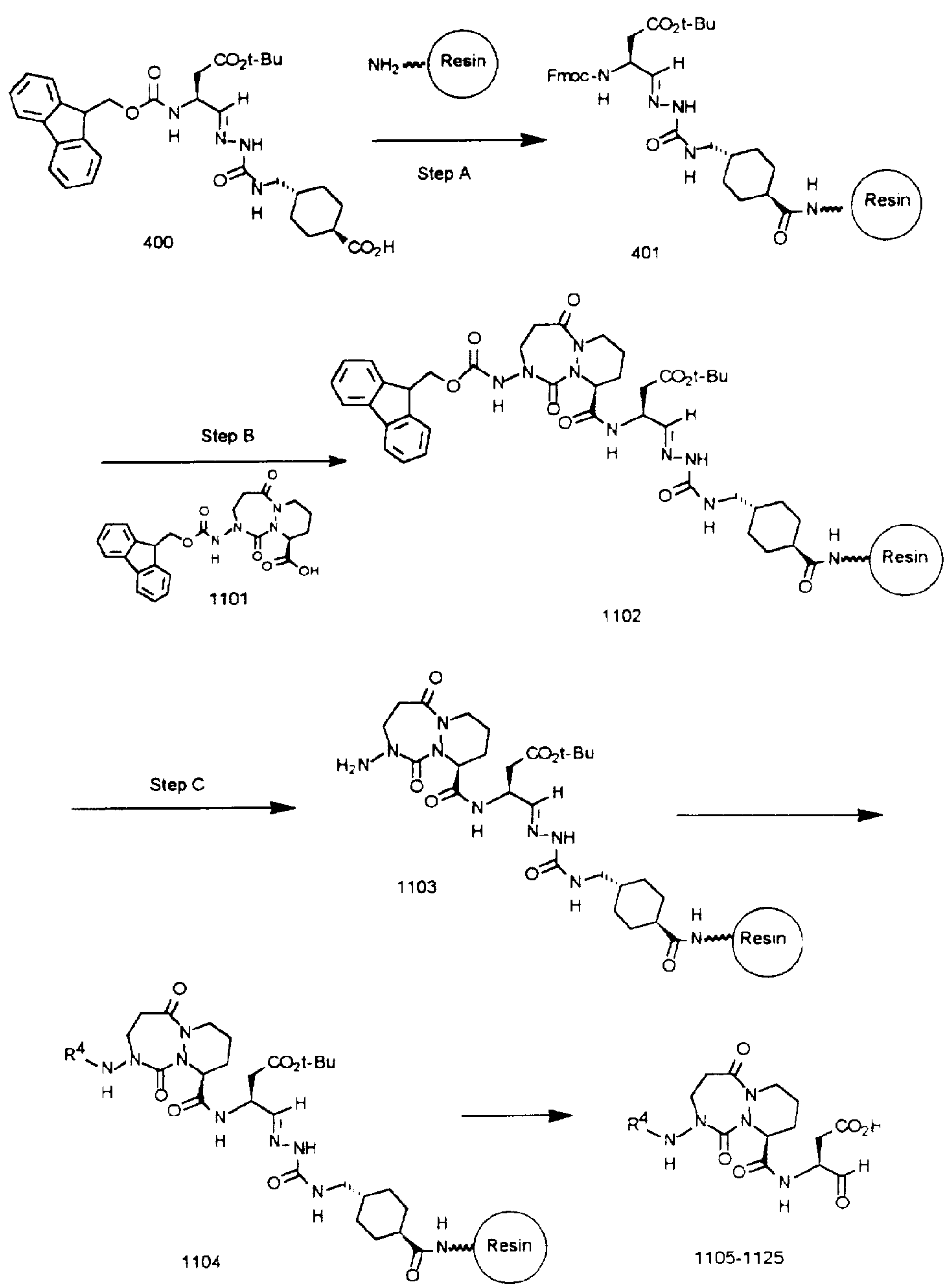
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1116		C23H25N5O9	515.48	14.144 (1) 85%	538.8
1117		C24H29N5O8	515.53	11.551 (2) 97%	538.8

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1118		C21H31N5O7	465.51	13.974 (1) 96%	488.9
1119		C22H33N5O7	479.54	11.079 (2) 95%	502.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1120		C21H23ClN6O8	522.91	16.796 (1) 99%	547.3
1121		C22H25N5O9	503.47	11.131 (1) 99%	527.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1122		C24H31N5O7	501.54	10.892 (2) 98%	525.5
1123		C26H24N4O10	552.50	15.85 >0.98	574

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1124		C24H29N5O11	563.53	13.336 (1) 99%	587
1125		C21H23Cl2N5O8	544.35	8.99 0.95	566



Step A. Synthesis of 401. TentaGel S® NH_2 resin (0.25 mmol/g, 5.25 g) was placed in a sintered glass shaker vessel and washed with dimethylacetamide (3 X 15 mL). Compound **400** (1.36 g, 2.3 mmol) was

dissolved in DMA (10 mL) and O-benzotriazole-N,N,N,N'-tetramethyluronium hexafluorophosphate (HBTU; 0.88 g, 2.3 mmol), and DIEA (0.8 mL, 4.6 mmol) were added. The solution was transferred to the resin and a further 5 mL DMA added. The reaction mixture was agitated for 1.5 h at room temperature using a wrist arm shaker. The resin was filtered and washed with dimethylacetamide (4 X 15 mL).

Step B. Synthesis of 1102. Resin **401** was deprotected with 20% (v/v) piperidine/dimethylacetamide (15 mL) for 10 min (shaking) and then for 10 min with fresh piperidine reagent (15 ml). The resin was then washed with dimethylacetamide (6 X 15 ml), followed by N-methypyrrolidone (2 X 25 mL).

Compound **1101** (0.979 g, 2.11 mmol) was dissolved in dimethylacetamide (8 mL). HBTU (0.81 g, 2.1 mmol) and DIEA (0.75 mL, 4.3 mmol) were added and the solution added to the resin, followed by dimethylacetamide (4 mL). The reaction mixture was agitated for 2 h at room temperature using a wrist arm shaker. The resin work-up was performed as described for **401** to yield **1102**.

Step C. Synthesis of 1103. This compound was prepared from resin **1102** (0.040 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (2 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **1103**. The resin was washed with

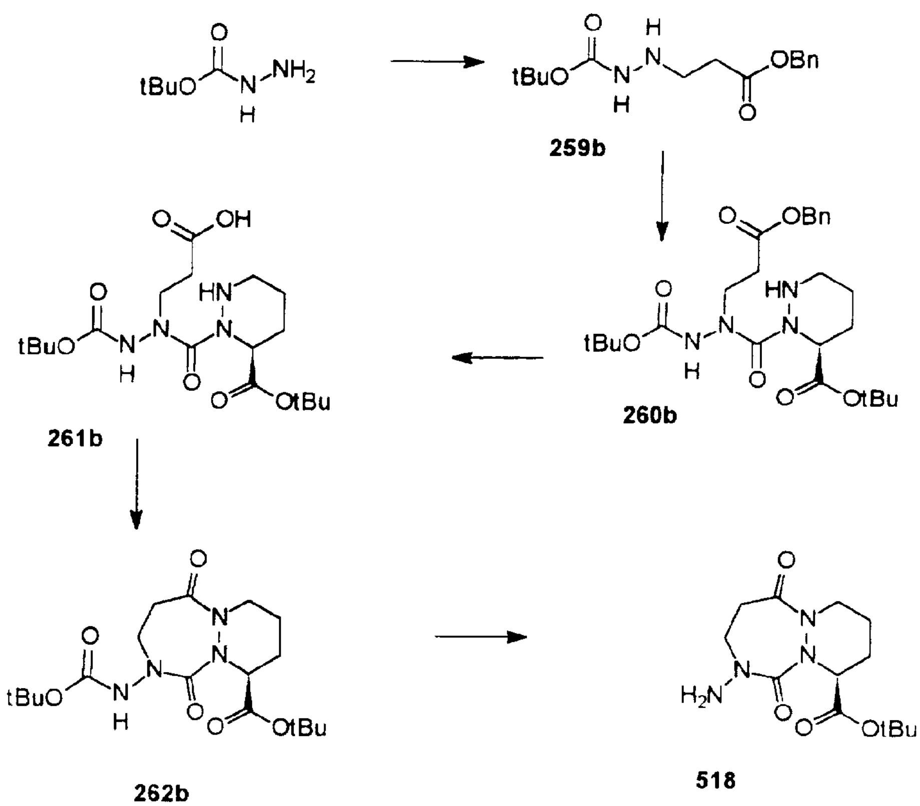
dimethylformamide (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL).

Resin **1103** was acylated with a solution of 0.4M carboxylic acid and 0.4M HOBT in N-methypyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.25 mL) and the reaction was shaken for 2 hr at room temperature. The acylation step was repeated. Finally, the resin was washed with N-methylpyrrolidone (1 X 1 mL), dimethylformamide (4 X 1 mL), dichloromethane (5 X 1 mL) and dried *in vacuo*. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H_2O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 ether:hexane (10 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% acetonitrile/90% H_2O/0.1% TFA (5 mL) and lyophilized to obtain crude **1105-1125** as a white powder. The compound was purified by semi-preparative RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (8% - 48%) containing 0.1% TFA (v/v) over 30 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **1105-1125** (10.8 mg, 63%).

Analytical HPLC methods:

(1) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm). Linear acetonitrile gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

(2) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm). Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.



Benzyl 3-(N'-t-butyloxycarbonylhydrazino)propionate (259b), was synthesized via method used to prepare **259** from **258** to afford a waxy solid (87g, 51%): mp 54-55°C; IR (film) 3324, 2978, 1732, 1713, 1455, 1367, 1277,

1254, 1171; ^{1}H NMR ($CDCl_3$) δ 7.35 (5H, m), 6.15 (1H, bs), 5.13 (2H, s), 3.15 (2H, t, J = 6.5), 2.54 (2H, t, J = 6.5), 1.45 (9H, s). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.29; H, 7.51; N, 9.51. MS (ES^+) 295 (M^+ + 1).

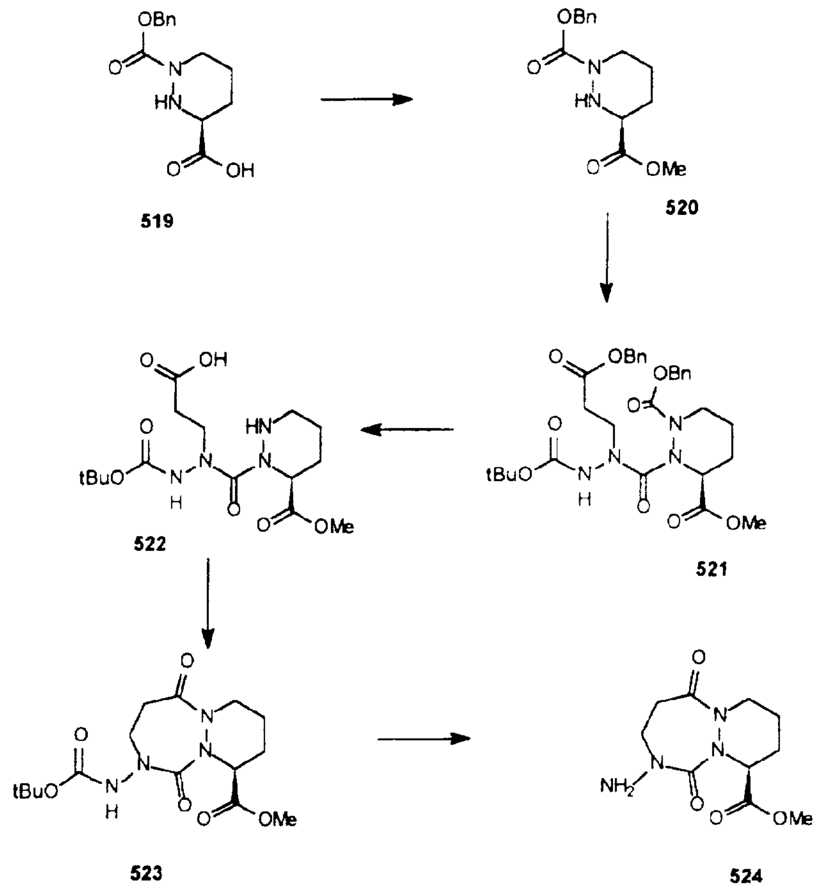
(3*S*) 1-Benzyl 3-t-butyl 2-(N-2-benzyloxycarbonylethyl-NI-2-butoxycarbonylhydrazino)carbonyl hexahydropyridazine dicarboxylate (260b), was synthesized via method used to prepare **260** from **259** to afford a gum (81g) which was used in the next step without purification. Analytical data for a pure sample: IR (film) 3318, 2976, 1733, 1451, 1412, 1393, 1366, 1256, 1161; ^{1}H NMR ($CDCl_3$) δ 7.34 (10H, m), 6.68 (0.5H, bs), 5.11 (4H, m), 4.63 (0.5H, bs), 4.14 (1H, m), 3.53 (2H, m), 3.08 (1H, m), 2.63 (2H, m), 2.10-1.60 (4H, m), 1.60-1.35 (19H, m + 2 x s).

(3*S*) t-Butyl 2-(N'-t-butoxycarbonyl-N-2-carboxyethylhydrazino)-carbonylhexahydropyridazine 3-carboxylate (261b), was synthesized via method used to prepare **261** from **260** to give a gum which was purified by flash chromatography (1:1 ethyl acetate/dichloromethane) to give the title compound **261b** (36.0g, 79.4% over 2 stages): IR (film) 3267, 2979, 2937, 1728, 1668, 1394, 1369, 1245, 1159; ^{1}H NMR ($CDCl_3$) δ 7.6 (1H, bs), 6.8 (1H, vbs), 4.47 (1H, bs), 3.73 (2H, bs), 2.98 (1H, bs), 2.66 (3H, m), 2.04 (1H, bs), 1.84 (1H, m), 1.6-1.2 (21H, m + s).

(4*S*) t-Butyl 7-t-butoxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-

pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262b), was synthesized via method used to prepare **262** from **261** to give the title compound **262b**, (18.6g, 54%) as an oil: $[\alpha]_D^{20}$ +47.7° (c 0.236, CH_2Cl_2); IR (film) 3291, 2978, 1738, 1727, 1690, 1678, 1439, 1243, 1164; ^{1}H NMR ($CDCl_3$) δ 6.59 (1H, s), 5.06 (1H, m), 4.47 (1H, m), 3.85 (3H, m), 2.82 (1H, m), 2.37 (1H, m), 2.22 (1H, m), 1.92 (1H, m), 1.63 (2H, m), 1.48 and 1.46 (18H, 2 x s). MS (ES^+) 399 (M^+ + 1).

(4*S*) t-Butyl 7-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (518). Compound **262b** (2.43g, 6.1mmol) was dissolved in 1M hydrogen chloride in ethyl acetate (30ml) and stirred at room temperature for 20h. Solid sodium bicarbonate (4g, 46.5mmol) and water 20ml were added and the mixture stirred for 5min before separating and extracting the aqueous portion with ethyl acetate. The combined organic solution was washed with water, saturated salt, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (50% ethyl acetate in dichloromethane - 100% ethyl acetate) gave the pure product **518** (1.08g, 59%) as an unstable oil: $[\alpha]_D^{20}$ +82° (c 0.55, CH_2Cl_2); IR (film) 3331, 2977, 1731, 1680, 1664, 1439, 1420, 1315, 1158; ^{1}H NMR ($CDCl_3$) δ 5.08 (1H, m), 4.48 (1H, m), 3.80 (2H, Abq), 3.70 (2H, bs, exch with D_2O), 3.53 (1H, m), 2.75 (1H, m), 2.30 (2H, m), 1.88 (1H, m), 1.71 (2H, m), 1.47 (9H, s).



(3*S*) Methyl 1-benzyloxycarbonyl-hexahydropyridazine-3-carboxylate (520). **519** (9.4g, 35.6mmol) was suspended in methanol (230ml) and cooled to 0°C in an ice bath. Thionyl chloride (3ml, 4.89g, 41.1mmol) was added dropwise over 30min and the mixture stirred at ambient temperature for 48h. The solvent was removed in vacuo at 30°C and the oily residue dissolved in ethyl acetate (500ml). The organic solution was washed with saturated sodium bicarbonate, water and brine, dried ($MgSO_4$) and concentrated to give **520** (7.84g, 79%) as an oil: $[\alpha]_D^{22}$ -25.9° (c 0.615, CH_2Cl_2); IR (film) 2953, 1739, 1703, 1694, 1440, 1403, 1357, 1261, 1241, 1174; ^1H NMR ($CDCl_3$) δ 7.36 (5H, s), 5.18 (2H, s), 4.00 (1H,

bd), 3.73 (3H, s), 3.55 (1H, dd), 3.12 (1H, t), 2.06 (1H, m), 1.73 (3H, m). Anal. Calcd for $C_{14}H_{17}N_2O_4 \cdot 0.25H_2O$: C, 59.46; H, 6.59; N, 9.91. Found: C, 59.44; H, 6.46; N, 10.09.

(3*S*) 1-Benzyl 3-methyl 2-(N-2-benzyloxycarbonylethyl-NI-t-butoxycarbonylhydrazino)carbonyl hexahydropyridazine dicarboxylate (521). Using a similar method to that described for **260** above, **521** was prepared, 96% as a crude oil: $[\alpha]_D^{22}$ -22.16° (c 0.25, CH_2Cl_2); IR (film) 3316, 2976, 2953, 1738, 1726, 1714, 1690, 1367, 1260, 1167; ^1H NMR ($CDCl_3$) δ 7.25 (10H, m), 6.82 (1H, bs), 5.10 (4H, m), 4.80 (1H, bs), 4.3-3.4 (6H, m), 3.10 (1H, m), 2.59 (2H, m), 1.95 (2H, m), 1.44 (10H, m + s).

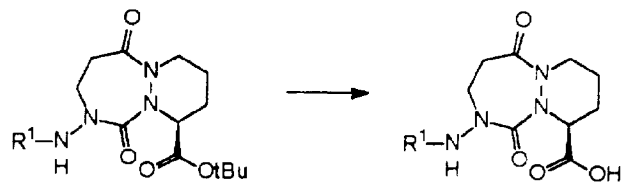
(3*S*) Methyl 2-(N'-t-butoxycarbonyl-N-2-carboxyethylhydrazino)-carbonyl hexahydropyridazine 3-carboxylate (522). Using a similar method to that described for **261** above, **522** was prepared, 92% as a white solid: mp. 146-148°C (decomp); $[\alpha]_D^{22}$ +27.8° (c 0.25, CH_2Cl_2); IR (KBr) 3346, 1740, 1710, 1626, 1497, 1290, 1250, 1206, 1179, 1159; ^1H NMR ($CDCl_3$) δ 7.60 (1H, bs), 7.5-5.5 (1H, vbs), 4.64 (1H, bs), 3.76 (5H, m + s), 3.00 (1H, m), 2.70 (3H, m), 2.16 (1H, m), 1.92 (1H, m), 1.56 (1H, m), 1.46 (11H, m + s). Anal. Calcd for $C_{15}H_{26}N_4O_7$: C, 48.12; H, 7.00; N, 14.96. Found: C, 48.21; H, 6.96; N, 14.86. MS (ES^+) 373 (M^- - 1).

(4*S*) Methyl 7-t-butoxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (523).

522 (7.15g, 19.1mmol) was dissolved in dichloromethane(100ml), containing dimethylformamide (0.5ml), and cooled to 0°C. Thionyl chloride (1.6ml, 2.61g, 22mmol) and N-ethyl morpholine (4.86ml, 440mg, 38.2mmol) were added and the mixture stirred for 2h. The organic mixture was washed with 2M sodium bisulphate (50ml), saturated sodium bicarbonate (50ml) and brine (50ml), dried ($MgSO_4$) and concentrated. The residues were triturated with ether to give **523** as a white solid (5.73g, 84%): mp. 186-188°C (decomp); $[\alpha]_D^{22}$ +65.3° (c 0.25, CH_2Cl_2); IR (KBr) 3298, 2978, 1750, 1720, 1682, 1658, 1455, 1423, 1369, 1316, 1241, 1212, 1160; ^1H NMR ($CDCl_3$) δ 6.56 (1H, s), 5.17 (1H, dd), 4.48 (1H, bd), 3.81 (3H, m), 3.75 (3H, s), 2.83 (1H, dt), 2.40 (1H, m), 2.28 (1H, m), 1.95 (1H, m), 1.67 (1H, m), 1.47 (9H, s). Anal. Calcd for $C_{15}H_{24}N_4O_6 \cdot 1/6H_2O$: C, 50.13; H, 6.82; N, 15.59. Found: C, 50.12; H, 6.71; N, 15.58. MS (ES^+) 357 (M^+ - 1, 46%), 301 (100%).

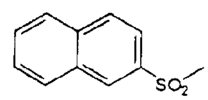
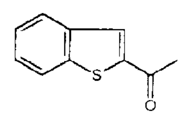
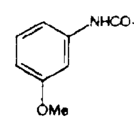
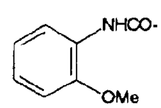
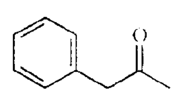
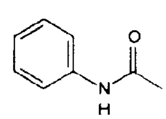
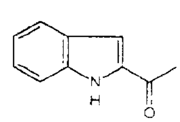
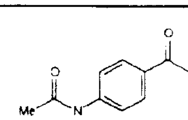
(4S) Methyl 7-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (524), was synthesized from **523** via method used to prepare **518**.

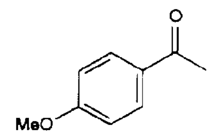
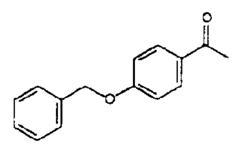
Compounds **262a-k** were synthesized via methods used to prepare **211b-f**.



262 263

262a-k 263a-k

compound	R
262a 263a	
262b 263b	
262c 263c	
262d 263d	
262e 263e	
262f 263f	
262g 263g	
262h 263h	

262i **263i**	
262j **263j**	$PhSO_2$—
262k **263k**	

(4*S*) t-Butyl 6,10-dioxo-7-(2-naphthyl)sulfonamide-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262a). 443mg (91%) of the title compound was obtained: mp. 56-7°C; $[\alpha]_D^{25}$ +76° (c 0.15, CH_2Cl_2); IR (KBr) 3429, 2979, 1734, 1675, 1418, 1369, 1339, 1323, 1244, 1164, 665; ^{1}H NMR ($CDCl_3$) δ 8.45 (1H, s), 8.00-7.59 (7H, m), 4.69-4.65 (1H, m), 4.25-4.12 (1H, m), 4.10-3.99 (1H, m), 3.73-3.55 (2H, m), 2.40-2.30 (1H, m), 1.99-1.91 (1H, m), 1.82-1.62 (2H, m), 1.48-1.46 (2H, m), 1.37 (9H, s). Anal. Calcd for $C_{23}H_{28}N_4O_6S \cdot H_2O$: C, 54.53; H, 5.97; N, 11.06. Found: C, 54.60; H, 5.73; N, 10.95. MS (ES^+) 489.

(4*S*) t-Butyl 6,10-dioxo-7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262c), 120mg (80%) of colourless foam was obtained:

$[\alpha]_D^{22}$ +22.6° (c 0.1, CH_2Cl_2); IR (KBr) 3316, 1732, 1671, 1609, 1551, 1495, 1455, 1432, 1316, 1288, 1245, 1218, 1158, 1122, 1023; ^1H NMR ($CDCl_3$) δ 7.16 (4H, m), 6.79 (1H, m) 6.60 (1H, m), 5.11 (1H, m), 4.59 (1H, m), 3.89 (2H, m), 3.77 (3H, s), 3.72 (2H, m), 2.85 (1H, m).

(4*S*) t-Butyl 6,10-dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a][1,2,4]triazepine-4-carboxylate (262d), (81%) was obtained as colourless foam: $[\alpha]_D^{22}$ +3.7° (c 0.1, CH_2Cl_2); IR (KBr) 3468, 3446, 3269, 1734, 1698, 1667, 1609, 1555, 1490, 1461, 1433, 1423, 1296, 1246, 1215, 1173, 1157, 1028, 756; ^1H NMR ($CDCl_3$) δ 8.23 (1H, m), 7.95 (1H, s), 6.95 (4H, m), 5.15 (1H, m), 4.60 (1H, m), 3.98-3.65 (4H, m), 3.89 (3H, s), 2.90 (1H, m), 2.48 (1H, m), 2.25 (1H, m), 2.05-1.65 (2H, m), 1.48 (9H, s).

(4*S*) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262e), was obtained as a white foamy solid (155mg, 53%): mp. 53-7°C; $[\alpha]_D^{22}$ +57.4° (c 0.1, CH_2Cl_2); IR (KBr) 3271, 2978, 1733, 1680, 1437, 1314, 1245, 1156; ^1H NMR ($CDCl_3$) δ 7.46 (1H, s), 7.42-7.20 (5H, m), 5.03 (1H, dd), 4.52-4.40 (1H, m), 3.96-3.70 (2H, m), 3.70-3.49 (1H, m), 3.63 (2H, s), 2.92-2.75 (1H, m), 2.43-2.33 (1H, m), 2.33-2.15 (1H, m), 2.00-1.50 (3H, m), 1.45 (9H, s). Anal. Calcd for $C_{21}H_{28}N_4O_5 \cdot 0.25H_2O$: C, 59.91; H, 6.82; N, 13.31. Found: C, 60.19; H, 6.80; N, 13.30. MS (ES^+) 418 (M^+ + 2, 25%), 417 (M^+ + 1, 100), 362 (9), 361 (45).

(4*S*) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262f), was obtained as a white solid (273mg, 93%): mp. 102-6°C; $[\alpha]_D^{22}$ +7.5° (c 0.07, CH_2Cl_2); IR (KBr) 3320, 2979, 1731, 1676, 1669, 1601, 1549, 1444, 1314, 1240, 1156; ^{1}H NMR ($CDCl_3$) δ 7.37-7.20 (6H, m), 7.08-6.98 (1H, m), 5.12 (1H, dd), 4.64-4.55 (1H, m), 4.02-3.78 (2H, m), 3.75-3.65 (1H, m), 2.94-2.75 (1H, m), 2.57-2.35 (1H, m), 2.35-2.20 (1H, m), 2.00-1.50 (3H, m), 1.48 (9H, s). Anal. Calcd for $C_{20}H_{27}N_5O_5 \cdot 0.4H_2O$: C, 56.56; H, 6.60; N, 16.49. Found: C, 56.89; H, 6.58; N, 16.07. MS (ES$^+$) 419 (M$^+$ + 2, 24%), 418 (M$^+$ + 1, 100), 363 (15), 362 (81), 242 (10).

(4*S*) t-Butyl 6,10-dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a][1,2,4]triazepine-4-carboxylate (262g), (13g) was obtained as a white solid (298mg, 70%): mp. 138-43°C; $[\alpha]_D^{23}$ +69.8° (c 0.1, CH_2Cl_2); IR (KBr) 3282, 2978, 1733, 1664, 1536, 1421, 1310, 1156, 748; ^{1}H NMR ($CDCl_3$) δ 9.67 (1H, s), 9.53 (1H, s), 7.50 (1H, d), 7.30-7.15 (2H, m), 7.10-7.00 (1H, m), 6.93 (1H, s), 5.16-5.12 (1H, m), 4.60-4.50 (1H, m), 4.05-3.85 (2H, m), 3.85-3.70 (1H, m), 3.05-2.90 (1H, m), 2.55-2.35 (1H, m), 2.35-2.20 (1H, m), 2.00-1.85 (1H, m), 1.85-1.50 (2H, m), 1.47 (9H, s). Anal. Calcd for $C_{22}H_{27}N_5O_5 \cdot 0.45H_2O$: C, 58.77; H, 6.26; N, 15.58. Found: C, 59.14; H, 6.24; N, 15.18. MS (ES$^+$) 433 (M$^+$ + 2, 26%), 442 (M$^+$ + 1, 100), 387 (17), 386 (79), 285 (20), 229 (85), 211 (26), 185 (15), 183 (57), 139 (9).

(4*S*) t-Butyl 7-[(4-acetamido)benzamido]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxylate (262h), was obtained as a white solid (325mg, 73%): mp. 209-12°C; $[\alpha]_D^{24}$ +62.4° (c 0.2, CH_2Cl_2); IR (KBr) 3513, 3269, 2980, 1731, 1680, 1653, 1599, 1531, 1314, 1158; ^1H NMR ($CDCl_3$) δ 9.40 (1H, s), 8.75 (1H, s), 7.72 (2H, d), 7.47 (2H, d), 5.15-5.05 (1H, m), 4.55-4.45 (1H, m), 4.05-3.70 (3H, m), 3.00-2.80 (1H, m), 2.45-2.35 (1H, m), 2.30-2.15 (1H, m), 2.10 (3H, s), 2.00-1.80 (1H, m), 1.80-1.50 (2H, m), 1.48 (9H, s). Anal. Calcd for $C_{22}H_{29}N_5O_6$: C, 57.51; H, 6.36; N, 15.24. Found: C, 57.41; H, 6.38; N, 15.12. MS (ES^+) 461 (M^+ + 2, 26%), 460 (M^+ + 1, 100), 405 (12), 404 (55), 354 (7), 285 (23), 229 (52), 183 (22).

(4*S*) t-Butyl 6,10-dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-carboxylate (262i), was obtained as a white glassy solid (76%): mp. 85-9°C; $[\alpha]_D^{25}$ +66.4° (c 0.11, CH_2Cl_2); IR (KBr) 1732, 1668, 1607, 1502, 1440, 1312, 1295, 1258, 1176, 1157, 1025; ^1H NMR ($CDCl_3$) δ 8.25 (1H, s), 7.77 (2H, m), 6.90 (2H, m), 5.11-5.07 (1H, m), 4.55-4.48 (1H, m), 4.01-3.91 (2H, m), 3.86-3.78 (1H, m), 3.85 (3H, s), 2.98 (1H, m), 2.46-2.40 (1H, m), 2.26-2.20 (1H, m), 2.05-1.80 (1H, m), 1.70-1.64 (2H, m), 1.48 (9H, s).

(4*S*) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262j), was obtained as a white crystalline solid (79%): mp. 182-3°C (dec); $[\alpha]_D^{22}$ +92.1° (c 0.4, CH_2Cl_2);

IR (KBr) 3283, 1732, 1684, 1448, 1430, 1404, 1369, 1338, 1306, 1285, 1242, 1169, 1091, 692; ^{1}H NMR ($CDCl_3$) δ 7.89 (2H, d, J = 7.4), 7.76 (1H, s), 7.64-7.49 (3H, m), 4.83 (1H, m), 4.35 (1H, brd, J = 13.0), 4.00 (1H, m), 3.74-3.63 (2H, m), 2.39-2.26 (2H, m), 2.06 (1H, m), 1.50-1.41 (10H, m). Anal. Calcd for $C_{19}H_{26}SN_4O_6$: C, 52.04; H, 5.98 N, 12.78. Found: C, 52.11; H, 5.95; N, 12.71. MS (ES^+) 437 (M^+ - 1, 100%).

(3*S*) t-Butyl (7-(4-benzyloxyphenyl)carbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a][1,2,4]triazepine-4-carboxylate (262k), (83%) was obtained: $[\alpha]_D^{22}$ +42.3°. (c 0.11, CH_2Cl_2);.IR (KBr) 3287, 2997, 2935, 1735, 1681, 1606, 1501, 1296, 1248, 1173,1155. ^{1}H NMR ($CDCl_3$) δ 9.23 (1H, s), 7.73 (2H, d), 7.38 (5H, m), 6.85 (2H, d), 5.08 (1H, m), 5.02 (2H, s), 4.48 (1H, bd), 4.15-3.65 (3H, m), 2.96 (1H, m), 2.45-2.10 (2H, m), 1.88 (1H, m), 1.63 (2H, m), 1.48 (9H, s). M.S. (ES^+ 509 (M^++1).

Compounds **263a-k** were synthesized via methods used to prepare **212b-f**.

(4*S*) 6,10-Dioxo-7-(2-naphthalenesulfonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263a), 348mg (94%) obtained as a white foamy solid: mp. $[\alpha]_D^{21}$ +171° (c 0.056, CH_2Cl_2); IR (KBr) 3426, 3233, 2953, 1734, 1663, 1481, 1415, 1340, 1214, 1167, 1132, 1075, 668; ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, s), 8.00-7.60 (7H, m), 4.85-4.83 (1H, m), 4.25-4.00 (1H, m), 4.07-3.90 (1H, m), 3.70-3.46 (2H, m), 2.38-2.30 (1H, m), 2.12-

2.01 (1H, m), 1.91-1.83 (1H, m), 1.46-1.26 (1H, m), 1.13-1.06 (1H, m), 0.90-0.77 (1H, m). MS (ES^+) 431.

(4*S*) 7-(Benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263b). 200mg (100%) was obtained as a white solid: mp. 155°C; $[\alpha]_D^{20}$ +13° (c 0.07, CH_2Cl_2); IR (KBr) 3431, 2935, 1734, 1663, 1531, 1435, 1292, 1177; ^1H NMR ($CDCl_3$) δ 9.73 (1H, bs), 7.73-7.27 (5H, m), 5.35-5.25 (1H, m), 4.56-4.48 (1H, m), 4.05-3.65 (3H, m), 3.12-3.00 (1H, m), 2.50-2.45 (1H, m), 2.30-2.20 (1H, m), 2.10-2.00 (1H, m), 1.75-1.61 (2H, m). MS (ES^+) 401.

(4*S*) 6,10-Dioxo-7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263c), 216mg, (100+%) obtained as a colourless foam: $[\alpha]_D^{23}$ 32.5° (c 0.1, CH_2Cl_2); IR (KBr) 3326, 1730, 1661, 1610, 1555, 1495, 1431, 1314, 1288, 1217, 1175, 1161; ^1H NMR ($CDCl_3$) δ 7.87 (1H, s), 7.58 (1H, s), 7.19 (2H, m), 6.82 (1H, m), 6.62 (1H, m), 5.21 (1H, m), 4.55 (1H, m), 3.76 (3H, s), 4.0-3.65 (4H, m), 2.85 (1H, m), 2.35 (2H, m), 1.75 (1H, m), 1.71 (2H, m).

(4*S*) 6,10-Dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263d), (100+%) obtained as colourless foam: $[\alpha]_D^{24}$ +11.7° (c 0.1, CH_2Cl_2); IR (KBr) 3394, 3325, 1666, 1603, 1543, 1490, 1463, 1438, 1329, 1311, 1292, 1249, 1214, 1176, 1119, 1024, 752; ^1H NMR ($CDCl_3$) δ 8.15 (1H,

m), 7.97 (2H, m), 7.15-6.84 (3H, m), 5.29 (1H, m), 4.62 (1H, m), 4.04-3.65 (4H, m), 3.89 (3H, s), 2.92 (1H, m), 2.50 (1H, m), 2.30 (1H, m), 2.10-1.75 (2H, m).

(4*S*) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetyl-amino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263e), obtained as a white foamy solid (117mg, 98%): mp. 109-14°C; $[\alpha]_D^{24}$ +82.6° (c 0.06, CH_2Cl_2); IR (KBr) 3700-2250 (br), 3437, 3274, 2959, 1733, 1664, 1481, 1437, 1310, 1177; ^1H NMR ($CDCl_3$) δ 7.99 (1H, s), 7.40-7.15 (5H, m), 5.15-5.10 (1H, m), 5.25-4.70 (1H, bs), 4.50-4.35 (1H, m), 3.95-3.50 (3H, m), 3.61 (2H, s), 2.93-2.78 (1H, m), 2.40-2.20 (2H, m), 2.10-1.80 (1H, m), 1.80-1.60 (2H, m). Anal. Calcd for $C_{17}H_{20}N_4O_5 \cdot 1H_2O$: C, 53.96; H, 5.86; N, 14.81. Found: C, 54.12; H, 5.50; N, 14.68. MS (ES^+) 360 (M+, 21%), 359 (M^+ - 1, 100), 196 (14), 182 (14), 111 (7).

(4*S*) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263f), obtained as a white foamy solid (199mg, 92%): mp. 149-52°C; $[\alpha]_D^{24}$ +92.0° (c 0.01, CH_3OH); IR (KBr) 3700-2300 (br), 3319, 2956, 1726, 1664, 1600, 1548, 1500, 1444, 1313, 1238, 755; ^1H NMR (D_6-DMSO) δ 8.90 (1H, s), 8.24 (1H, s), 7.42 (2H, d), 7.30-7.20 (2H, m), 7.00-6.90 (1H, m), 4.98-4.92 (1H, m), 4.32-4.22 (1H, m), 3.80-3.55 (3H, m), 2.85-2.70 (1H, m), 2.30-2.20 (1H, m), 2.20-2.00 (1H, m), 1.90-1.35 (3H, m). Anal. Calcd for $C_{16}H_{19}N_5O_5 \cdot 0.75H_2O$: C, 51.26; H, 5.51; N, 18.68. Found: C, 51.11; H, 5.23; N,

18.42. MS (ES^+) 361 (M+, 20%), 360 (M^+ - 1, 100), 241 (11), 240 (89), 196 (15), 175 (29), 111 (12).

(4*S*) 6,10-Dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263g), was obtained as a white solid (259mg, 92%)mp. 248-51°C; $[\alpha]_D^{24}$ +94.0° (c 0.01, CH_3OH); IR (KBr) 3700-2300 (br) 3341, 2956, 1738, 1668, 1651, 1529, 1425, 1311, 1259, 751; ^1H NMR (D_6-DMSO) δ 13.29 (1H, bs), 11.72 (1H, s), 10.64 (1H, s), 7.65 (1H, d), 7.45 (1H, d), 7.26-7.15 (1H, m), 7.17 (1H, s), 7.10-7.00 (1H, m), 5.05-4.95 (1H, m), 4.40-4.25 (1H, m), 3.90-3.50 (3H, m), 2.88-2.75 (1H, m), 2.38-2.20 (1H, m), 2.20-2.00 (1H, m), 1.90-1.35 (3H). Anal. Calcd for $C_{18}H_{19}N_5O_5 \cdot 0.5H_2O$: C, 53.59; H, 5.25; N, 17.35. Found: C, 53.66; H, 4.88; N, 17.11. MS (ES^+) 385 (M+, 23%), 384 (M^+ - 1, 100), 298 (6), 253 (8), 227 (10), 199 (23), 196 (10), 173 (9), 126 (21).

(4*S*) 7-[(4-Acetamido)benzamido]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263h), was obtained as a white solid (282mg, 99%): mp. 210-5°C; $[\alpha]_D^{24}$ +74.5° (c 0.01, CH_3OH); IR (KBr) 3700-2300 (br) 3444, 3316, 2960, 1664, 1599, 1531, 1439, 1301, 1184; ^1H NMR (D_6-DMSO) δ 13.30 (1H, bs), 10.50 (1H, s), 10.25 (1H, s), 7.80 (2H, d), 7.68 (2H, d), 5.00-4.90 (1H, m), 4.35-4.25 (1H, m), 3.90-3.40 (3H, m), 2.88-2.70 (1H, m), 2.35-2.25 (1H, m), 2.25-1.95 (1H, m), 2.08 (3H, s), 1.95-1.35 (3H, m). MS (ES^+) 403

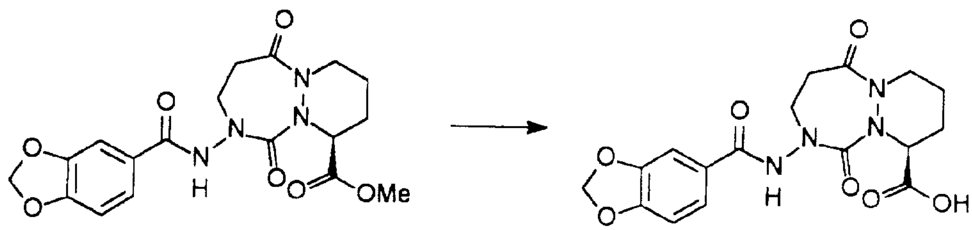
(M+, 10%), 402 (M^+ - 1, 100), 358 (10), 247 (10), 227 (16), 219 (51), 198 (12), 184 (17).

(4*S*) 6,10-Dioxo—7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-carboxylic acid (263i), was obtained as a white glassy solid (approx 100%) used without purification: ^{1}H NMR ($CDCl_3$) δ 9.23 (1H, s), 7.72 (2H, d, J = 8.8), 6.81 (2H, d, J = 8.9), 5.22 (1H, m), 4.51 (1H, m), 3.97-3.72 (2H, m), 3.81 (3H, s), 3.03 (1H, m), 2.51-2.46 (1H, m), 2.31-2.25 (1H, m), 2.03 (1H, m), 1.72 (2H, m).

(4*S*) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263j), was obtained as a white solid (100%): mp. 73-83°C (dec); $[\alpha]_D^{22}$ +104.7° (c 0.3, CH_2Cl_2); IR (KBr) 3600-2500 (br), 3208, 1734, 1666, 1481, 1448, 1416, 1338, 1311, 1214, 1171, 1091, 729, 689; ^{1}H NMR ($CDCl_3$) δ 7.87 (3H, m), 7.70-7.50 (3H, m), 7.16 (1H, brs), 4.99 (1H, m), 4.37 (1H, brd, J = 12.8), 3.92 (1H, m), 3.67 (2H, m), 2.36 (2H, m), 2.13 (1H, brd, J = 12.2), 1.56 (3H, m). Anal. Calcd for $C_{15}H_{18}SN_4O_6 \cdot 0.25CF_3CO_2H$: C, 45.31; H, 4.48 N, 13.64. Found: C, 45.48; H, 4.71; N, 13.43. MS (ES^+) 383 (MH^+, 100%). Accurate mass calculated for $C_{15}H_{19}SN_4O_6$ (MH^+): 383.1025. Found: 383.1007.

(4*S*) 7-(4-Benzyloxyphenyl)carbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263k), (100%) obtained: mp. 130-142°C; IR (KBr) 3272,

2945, 1738, 1650, 1611, 1501, 1445, 1309, 1255, 1171; ^{1}H NMR ($CDCl_3$) δ 9.35 (1H, s), 7.74 (2H, d), 7.38 (5H, m), 6.85 (2H, d), 5.40 (1H, bs), 5.19 (1H, s), 5.02 (2H, s), 4.49 (1H, d), 3.92 (2H, m), 3.68 (1H, m), 2.99 (1H, bs), 2.43 (1H, bs), 2.22 (1H, bs), 1.99 (1H, bs), 1.68 (2H, bs).

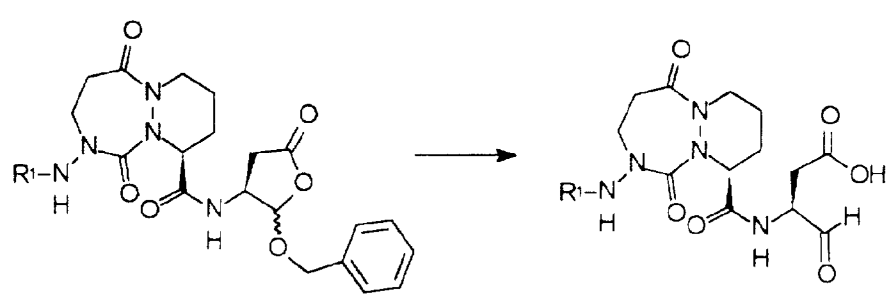


5251 2631

(4*S*) Methyl 6,10-dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (5251), was synthesized via method used to prepare **211** to afford a white crystalline solid (3.35g, 83%): mp. 214-5°C; $[\alpha]_D^{20}$ +75.2° (c 0.1, CH_2Cl_2); IR (KBr) 3272, 2955, 1747, 1664, 1610, 1485, 1443, 1265, 1040; ^{1}H NMR ($CDCl_3$) δ 8.66 (1H, s), 7.32 (1H, dd), 7.23 (1H, d), 6.76 (1H, d), 6.02 (2H, s), 5.20 (1H, dd), 4.55-4.45 (1H, m), 4.03-3.70 (3H, m), 3.78 (3H, s), 3.05-2.88 (1H, m), 2.47-2.35 (1H, m), 2.35-2.20 (1H, m), 2.10-1.90 (1H, m), 1.85-1.50 (2H, m). Anal. Calcd for $C_{18}H_{20}N_4O_7 \cdot 0.5H_2O$: C, 52.87; H, 5.06; N, 13.70. Found: C, 52.84; H, 5.00; N, 13.66. MS (ES^+) 406 (M^+ + 2, 20%), 405 (M^+ + 1, 100), 391 (10), 162 (6), 148 (3), 105 (2).

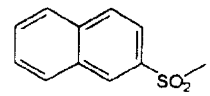
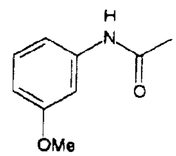
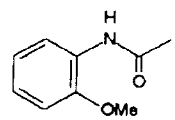
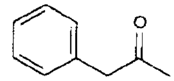
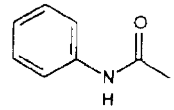
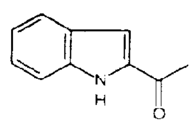
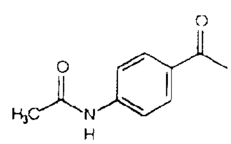
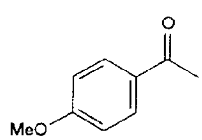
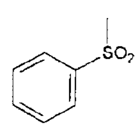
(4*S*) 6,10-Dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-

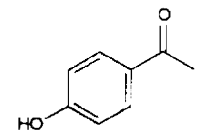
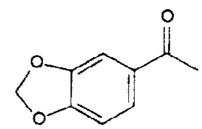
pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (2631). A suspension of **5251** (3.32g, 8.2mmol) in tetrahydrofuran (60ml) was treated with a solution of LiOH•H_2O (0.69g, 16.4mmol, 2.0 equiv) in water (20ml). The resulting mixture was stirred for 1h, concentrated and the residue dissolved in water (50ml). The solution was acidified using 2M. $NaHSO_4$ and the product extracted with EtOAc (100ml and 50ml portions). The combined extract was washed once with brine (2 x 50ml), dried ($MgSO_4$) and concentrated to afford **2631** as a white crystalline solid (2.87g, 90%): mp. 154-8°C; $[\alpha]_D^{20}$ +85.6° (c 0.01, CH_3OH); IR (KBr) 3700-2300 (br), 3248, 2942, 1733, 1681, 1658, 1648, 1536, 1486, 1440, 1297, 1255, 1037; ^1H NMR (D_6-DMSO) δ 13.23 (1H, bs), 10.45 (1H, s), 7.45 (1H, d), 7.35 (1H, s), 7.03 (1H, d), 6.12 (2H, s), 5.00-4.93 (1H, m), 4.35-4.25 (1H, m), 3.90-3.40 (3H, m), 2.95-2.70 (1H, m), 2.40-2.25 (1H, m), 2.15-2.00 (1H, m), 1.91-1.40 (3H, m). Anal. Calcd for $C_{17}H_{18}N_4O_7$•$0.8H_2O$: C, 50.45; H, 4.88; N, 13.84. Found: C, 50.80; H, 4.95; N, 13.36. MS (ES^+) 390 (M^+, 19%), 389 (M^+ - 1, 100), 345 (9), 204 (31), 182 (27), 111 (12).



264a, c-l

265a, c, d, f 1015, 1018, 1027, 1052, 1056, 1075, 1095

compound	R^1
264a 265a	
264c 265c	
264d 265d	
264e 1095	
264f 265f	
264g 1075	
264h 1018	
264i 1052	
264j 1027	

264k **1056**	
264l **1015**	

[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-7-(2-naphthalenesulfonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264a), was synthesized by a similar method as compound **213e** to afford a white solid (240mg, 82%): IR (KBr) 3380, 3066, 2947, 1789, 1750, 1691, 1454, 1417, 1368, 1298, 1262, 1235, 1193, 1118, 756, 696; ^{1}H NMR (D_6-DMSO) δ 8.59 (1H, d, J = 6.8), 8.48 (1H, s), 8.25-8.09 (3H, m), 7.85-7.75 (3H, m), 7.36 (5H, m), 5.39 (1H, m), 4.21 (2H, AB, J = 14.2), 4.53-4.49 (1H, m), 4.25-4.10 (2H, m), 3.65-3.44 (3H, m), 3.13-2.99 (1H, m), 2.43-2.16 (1H, m), 1.72-0.72 (7H, m). Anal. Calcd for $C_{30}H_{31}N_5O_8S$: C, 57.96; H, 5.03; N, 11.27. Found: C, 57.28; H, 5.14; N, 10.48. MS (ES^+) 622.

[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-1-carboxamide (264c), was prepared by a similar method as **213e**, (55%) as a colourless foam: mp. 135-40°C; $[\alpha]_D^{22}$ +51.6° (c 0.1, CH_2Cl_2); IR (KBr) 3314, 1790, 1664,

1608, 1543, 1496, 1455, 1428, 1325, 1287, 1250, 1218, 1160, 1118; ^{1}H NMR ($CDCl_3$) δ 8.00 (1H, d, J = 7.1), 7.66 (1H, s), 7.55 (1H, s), 7.28 (5H, m), 7.14 (2H, m), 6.87 (1H, d, J = 7.4), 6.59 (1H, m), 5.42 (1H, s), 4.66 (5H, m), 3.90-3.65 (4H, m), 3.73 (3H, s), 2.98 (2H, m), 2.38 (2H, m), 2.01-1.65 (3H, m).

[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-1-carboxamide (264d), was prepared by a similar method as **213e**, (72%) as colourless foam: $[\alpha]_D^{22}$ +21.4° (c 0.1, CH_2Cl_2); IR (KBr) 3302, 1791, 1689, 1678, 1664, 1602, 1536, 1489, 1461, 1437, 1420, 1249, 1119, 1023, 942, 751; ^{1}H NMR ($CDCl_3$) δ 8.07 (1H, d, J = 7.7), 7.82 (1H, s), 7.68 (1H, d, J = 6.7), 7.49 (1H, s), 7.34 (5H, m), 6.96 (3H, m), 5.47 (1H, s), 4.82 (2H, d + m, J = 11.5), 4.63 (1H, d, J = 11.5), 4.49 (2H, m), 3.85 (4H, s + m), 3.68 (2H, m), 3.01 (2H, m), 2.46 (2H, m), 1.95 (3H, m), 1.57 (1H, m).

[4*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264e) was synthesized via a similar method as used to prepare **213e** to afford a mixture of diastereomers (Syn:anti isomer ratio 9:1) as a white glassy solid (128mg, 78%): mp. 103-8°C; IR (KBr) 3419, 3302, 1793, 1664, 1535, 1421, 1327, 1256, 1123, 973; ^{1}H NMR (D_6-DMSO) δ 10.20 (0.9H, s), 9.35 (0.1H, s), 8.74 (0.1H, d), 8.49 (0.9H, d), 7.36-7.15 (10H, m), 5.67 (0.9H, d), 5.44 (0.1H, s),

4.85-4.75 (1H, m), 4.74-4.60 (1H, m), 4.77 and 4.63 (2H, dd), 4.30-4.10 (1H, m), 3.80-3.40 (3H, m), 3.43 (2H, s), 3.10-2.40 (3H, m), 2.25-2.15 (1H, m), 2.00-1.35 (4H, m). Anal. Calcd for $C_{28}H_{31}N_5O_7 \cdot 0.5H_2O$: C, 60.21; H, 5.77; N, 12.53. Found: C, 60.38; H, 5.83; N, 12.13. MS (ES^+) 551 (M^+ + 2, 33%), 550 (M^+ + 1, 100), 480 (7), 343 (8), 279 (4).

[4*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264f), was prepared by a similar method as compound **213e** to afford the pure syn-isomer as a white foamy solid (225mg, 82%): mp. 130-5°C; $[\alpha]_D^{24}$ +10.8° (c 0.1, CH_2Cl_2); IR (KBr) 3316, 1791, 1688, 1676, 1664, 1601, 1536, 1445, 1314, 1242, 973; ^1H NMR (D_6-DMSO) δ 8.84 (1H, s), 8.49 (1H, d), 8.19 (1H, s), 7.45-7.18 (9H, m), 7.00-6.90 (1H, m), 5.68 (1H, d), 4.90-4.81 (1H, m), 4.75-4.60 (1H, m), 4.78 and 4.63 (2H, dd), 4.30-4.20 (1H, m), 3.75-3.55 (3H, m), 2.85-2.55 (3H, m), 2.25-2.15 (1H, m), 2.00-1.35 (4H, m). Anal. Calcd for $C_{27}H_{30}N_6O_7 \cdot 0.5H_2O$: C, 57.95; H, 5.58; N, 15.02. Found: C, 58.12; H, 5.64; N, 14.81. MS (ES^+) 552 (M^+ + 2, 30%), 551 (M^+ + 1, 100), 362 (19), 299 (10), 279 (4).

[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264g), was prepared by a similar method as compound **213e** to afford the pure anti-isomer as a white solid (284mg, 80%): mp. 148-53°C; $[\alpha]_D^{24}$ -72.0° (c 0.1,

CH_2Cl_2); IR (KBr) 3404, 3295, 1789, 1660, 1536, 1421, 1310, 1260, 1122, 749; ^{1}H NMR (D_6-DMSO) δ 11.72 (1H, s), 10.58 (1H, s), 8.73 (1H, d), 7.65 (1H, d), 7.58-7.27 (6H, m), 7.27-7.10 (1H, m), 7.17 (1H, s), 7.10-7.00 (1H, m), 5.46 (1H, s), 4.90-4.85 (1H, m), 4.77 and 4.68 (2H, dd), 4.35-4.25 (2H, m), 3.95-3.55 (3H, m), 3.09 (1H, dd), 2.95-2.80 (1H, m), 2.47-2.25 (2H, m), 2.10-1.35 (4H, m). MS (ES$^+$) 574 (M+, 35%), 573 (M^+ - 1, 100), 384 (16), 383 (69), 341 (23), 327 (12), 267 (13), 200 (22).

[4*S*(2*RS*,3*S*)] 7-[(4-Acetamido)benzamido]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264h), was prepared by a similar method as compound **213e** to afford a mixture of diastereomers (Syn:anti isomer ratio 9:1) as a white solid (276mg, 70%): mp. 147-52°C; IR (KBr) 3444, 3304, 1793, 1665, 1602, 1531, 1505, 1423, 1294, 1264, 1181, 1123, 966; ^{1}H NMR (D_6-DMSO) δ 10.41 (1H, s), 10.22 (1H, s), 8.71 (0.1H, d), 8.48 (0.9H, d), 7.78 (2H, d), 7.67 (2H, d), 7.35-7.30 (5H, m), 5.68 (0.9H, d), 5.45 (0.1H, s), 4.88-4.80 (1H, m), 4.75-4.60 (1H, m), 4.77 and 4.63 (2H, dd), 4.30-4.20 (1H, m), 3.90-3.50 (3H, m), 3.10-2.50 (3H, m), 2.35-2.20 (1H, m), 2.07 (3H, s), 2.05-1.35 (4H, m). Anal. Calcd for $C_{29}H_{32}N_6O_8 \cdot 1H_2O$: C, 57.04; H, 5.61; N, 13.76. Found: C, 56.79; H, 5.50; N, 13.53. MS (ES$^+$) 594 (M^+ + 2, 34%), 593 (M^+ + 1, 100), 387 (8), 386 (38), 358 (8), 162 (19).

[4*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo—7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide

(264i), was prepared by a similar method to that described for compound **213e** to afford a white solid (70%): mp. 116-118°C; IR (KBr) 3315, 2951, 1793, 1664, 1607, 1502, 1258, 1177; ^{1}H NMR ($CDCl_3$) δ 8.07 (1H, s), 7.77 (2H, d, J = 8.6), 7.35 (5H, m), 6.94 (2H, d, J = 8.5), 6.74 (1H), 4.89 (1H, d, J = 11.1), 4.74 (1H, m), 4.60 (1H, d, J = 11.0), 4.48, 4.41 (1H, 2m), 3.86 (3H, s), 3.79, 3.71-3.53 (3H, 2m), 2.87 (2H, m), 2.44 (1H, m), 2.18, 1.91, 1.68 (5H, 3m).

[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264j), was synthesized by a similar method as compound **213e** to afford a foam (88%): $[\alpha]_D^{24}$ +74.2° (c 0.36, CH_2Cl_2); IR (KBr) 3332, 3235, 1793, 1664, 1537, 1448, 1416, 1337, 1169, 118, 1092, 940, 690; ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, s), 7.88 (2H, d, J = 6.8), 7.64-7.48 (3H, m), 7.34 (5H, s), 7.13 (1H, d, J = 6.9), 5.39 (1H, s), 4.81 (2H, m), 4.62 (1H, d, J = 11.5), 4.48 (1H, m), 4.33 (1H, m), 3.85 (1H, m), 3.59 (2H, m), 3.03 (1H, dd, J = 7.6, 18.2), 2.49-2.28 (3H, m), 1.94-1.40 (4H, m). Anal. Calcd for $C_{26}H_{29}SN_5O_8$: C, 54.63; H, 5.11 N, 12.25. Found: C, 54.42; H,5.28; N, 11.62. MS (ES^+) 572 (MH^+, 100%). Accurate mass calculated for $C_{26}H_{30}SN_5O_8$ (MH^+): 572.1815. Found: 572.1802.

[4*S*(2*RS*,3*S*)] 7-(4-Benzyloxyphenyl)carbonylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide

(264k), was prepared by the method used for **213e** (96%): IR (KBr) 3294, 2946, 1793, 1658, 1606, 1535, 1501, 1248, 1174, 1119. ^{1}H NMR ($CDCl_3$) δ 8.91 (1H, s), 7.85 (3H, m), 7.4 (10H, m), 7.02 (2H, d), 5.35 (1H, s), 5.10 (2H, s), 4.8-4.3 (5H, m), 4.00 (1H, bs), 3.78 (2H, m), 2.90 (2H, m), 2.5-1.5 (6H, m).

[4*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264l), was prepared by a similar method as compound **213e** to afford a mixture of diastereomers (syn:anti isomer ratio 1:1) as a white solid (1.72g, 71%): mp. 148-60°C; IR (KBr) 3314, 1780, 1677, 1658, 1651, 1550, 1485, 1439, 1258, 1132, 1038, 943; ^{1}H NMR (D_6-DMSO) δ 10.39 (1H, s), 8.71 (0.5H, d), 8.49 (0.5H, d), 7.44 (1H, d), 7.42-7.30 (6H, m), 7.03 (1H, d), 6.12 (2H, s), 5.68 (0.5H, d), 5.45 (0.5H, s), 4.90-4.82 (1H, m), 4.82-4.58 (2.5H, m), 4.40-4.10 (1.5H, m), 3.90-3.65 (2H, m), 3.65-3.43 (1H, m), 3.09 (0.5H, dd), 2.90-2.55 (1.5H, m), 2.45-2.10 (2H, m), 2.10-1.35 (4H, m). Anal. Calcd for $C_{28}H_{29}N_5O_9 \cdot 0.2H_2O$: C, 57.67; H, 5.08; N, 12.01. Found: C, 58.01; H, 5.33; N, 11.51. MS (ES$^+$) 581 (M^+ + 2, 33%), 580 (M+, 100), 374 (9), 373 (48), 345 (12), 261 (4), 239 (7), 149 (9).

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(2-naphthalenesulfonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (265a), was prepared by a similar method as compound **265** to afford a white solid (37mg,

17%): mp. 126-30°C (dec); $[\alpha]_D^{20}$ +30° (c 0.05, MeOH); IR (KBr) 3371, 2935, 1785, 1663, 1538, 1418, 1339, 1164, 669; ^{1}H NMR (CD_3OD) δ 8.44 (1H, s), 8.06-7.50 (7H, m), 7.22 (1H, d, J = 8.4), 4.58-4.57 (1H, m), 4.46-4.42 (1H, m), 4.16-4.09 (2H, m), 3.85-3.50 (3H, m), 2.84-2.78 (1H, m), 2.64-2.51 (1H, m), 2.44-2.15 (2H, m), 1.81-0.89 (4H, m). Anal. Calcd for $C_{23}H_{25}N_5O_8S{\bullet}H_2O$: C, 50.27; H, 4.95; N, 12.74. Found: C, 50.33; H, 5.04; N, 12.60. MS (ES^+) 530.

[3*S*(4*S*)] 3-[6,10-Dioxo—7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (265c), was prepared by a similar method as **265**, (90%) as a colourless solid: mp. ~150°C (decomp.); $[\alpha]_D^{23}$ +94.8° (c 0.1, 20% MeOH/CH_2Cl_2); IR (KBr) 3330, 1780, 1660, 1610, 1550, 1495, 1428, 1326, 1287, 1251, 1223, 1160; ^{1}H NMR (CD_3OD) δ 7.16 (2H, m), 6.89 (1H, d, J = 7.8), 4.58 (1H, m), 4.37 (2H, m), 3.76 (6H, s + m), 2.95 (1H, m), 2.67 (1H, m), 2.33 (1H, m), 2.20-1.85 (3H, m), 1.66 (1H, m).

[3*S*(4*S*)] 3-[6,10-Dioxo—7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxamido]-4-oxobutanoic acid (265d), was prepared by a similar method as **265**, (85%) as a colourless solid: mp. ~176-85°C; $[\alpha]_D^{23}$ +11.0° (c 0.1, MeOH); IR (KBr) 3392, 3328, 1784w, 1665, 1603, 1537, 1490, 1462, 1437, 1337, 1290, 1290, 1217, 1177, 1119, 1023; ^{1}H NMR (CD_3OD) δ 8.02 (2H, m), 6.95 (4H, m), 5.05 (1H, m), 4.60 (2H, m), 3.92 (4H, s + m), 3.00 (2H, m), 2.68 (1H, m), 2.39 (1H, m), 2.00 (4H, m), 1.69 (1H, m).

[3*S*(4*S*)] 3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (1095), was prepared by a similar method as compound **265** to afford a white solid (84mg, 90%): mp. 180-6°C; $[\alpha]_D^{22}$ +22.3° (c 0.065, CH_3OH); IR (KBr) 3700-2300 (br), 3287, 1664, 1536, 1425, 1261, 1181; ^1H NMR (CD_3OD) δ 7.35-7.20 (5H, m), 5.00-4.90 (1H, m), 4.60-4.50 (1H, m), 4.50-4.10 (2H, m), 3.90-3.50 (3H, m), 3.54 (2H, s), 3.00-2.80 (1H, m), 2.80-2.40 (2H, m), 2.35-2.20 (1H, m), 2.20-1.50 (4H, m). MS (ES^+) 459 (M+ 24%), 458 (M^+ - 1, 100), 358 (27), 175 (9), 149 (7), 137 (12). Accurate mass calculated for $C_{21}H_{26}N_5O_7$ (MH^+): 460.1832. found: 460.1840.

[3*S*(4*S*)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (265f), was prepared by a similar method as compound **265** to afford a white foamy solid (130mg, 88%): mp. 157-62°C; $[\alpha]_D^{24}$ +41.7° (c 0.1, CH_3OH); IR (KBr) 3700-2300 (br), 3325, 1782, 1663, 1547, 1443, 1315, 1242, 1181; ^1H NMR (CD_3OD) δ 7.40 (2H, dd), 7.35-7.20 (2H, m), 7.06-6.95 (1H, m), 5.05-4.95 (1H, m), 4.64-4.54 (1H, m), 4.50-4.35 (1H, m), 4.35-4.15 (1H, m), 3.90-3.69 (3H, m), 3.00-2.85 (1H, m), 2.80-2.45 (3H, m), 3.40-1.50 (4H, m). MS (ES^+) 460 (M+, 24%), 459 (M^+ - 1, 100), 341 (9), 340 (54), 296 (6), 239 (9).

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-

oxobutanoic acid (1075), was prepared by a similar method as compound **265** to afford a white solid (184mg, 83%): mp. 210-5°C; $[\alpha]_D^{24}$ +43.9° (c 0.1, CH_3OH); IR (KBr) 3700-2300 (br), 3309, 1660, 1537, 1423, 1311, 1262, 1184; ^1H NMR (CD_3OD) δ 7.61 (1H, d), 7.45 (1H, d), 7.28-7.15 (1H, m), 7.15-7.00 (1H, m), 7.13 (1H, s), 5.12-4.96 (1H, m), 4.62-4.55 (1H, m), 4.50-4.25 (2H, m), 4.00-3.69 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.25-1.50 (4H, m). MS (ES^+) 484 (M+, 26%), 483 (M^+ - 1, 100), 383 (25), 245 (12), 208 (11), 200 (21), 174 (31), 137 (18).

[3*S*(4*S*)] 3-{7-[(4-Acetamido)benzamido]-6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxamido}-4-oxobutanoic acid (1018), was prepared by a similar method as compound **265** to afford a white solid (177mg, 82%): mp. 235-40°C; $[\alpha]_D^{23}$ +27.3° (c 0.1, CH_3OH); IR (KBr) 3700-2300 (br), 3311, 2957, 1662, 1599, 1531, 1318, 1266, 1182; ^1H NMR (CD_3OD) δ 7.83 (2H, d), 7.69 (2H, d), 5.10-4.95 (1H, m), 4.64-4.55 (1H, m), 4.50-4.35 (1H, m), 4.32-4.22 (1H, m), 4.00-3.65 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.15 (3H, s), 2.15-1.50 (4H, m). Anal. Calcd for $C_{22}H_{26}N_6O_8 \cdot 1.5H_2O$: C, 49.90; H, 5.52; N, 15.87. Found: C, 50.21; H, 5.41; N, 15.49. MS (ES^+) 502 (M+, 28%), 501 (M^+ - 1, 100), 401 (8), 218 (4), 119 (2), 118 (5), 113 (16).

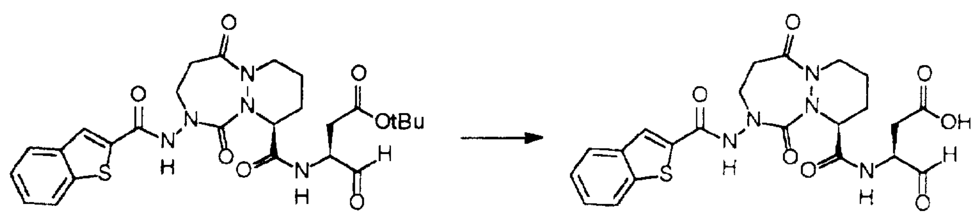
[3*S*(4*S*)] 3-[6,10-Dioxo—7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1052), was synthesized via method used to prepare **265** to afford a white solid

(0.194g, 100%): mp. 138-142°C; $[\alpha]_D^{20}$ +36.3° (c 0.19, CH_3OH); IR (KBr) 3434-2962, 1782, 1660, 1607, 1537, 1504, 1441, 1424, 1313, 1293, 1258, 1177; ^1H NMR (CD_3OD) δ 7.11 (2H, d, J = 8.8), 6.90 (2H, d, J = 8.9), 4.48 (1H, m), 4.34, 4.28 (1H, 2m), 4.15 (1H, m), 3.75 (3H, s), 3.75, 3.70 (3H, m), 2.88, 2.49, 2.28, 2.23, 2.00, 1.86, 1.79, 1.58 (8H, m).

[3*S*(4*S*)] 3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (1027), was synthesized by a similar method as compound **265** to afford a white foam (88%): $[\alpha]_D^{24}$ +22.6° (c 0.17, MeOH); IR (KBr) 3349, 1789, 1663, 1537, 1448, 1337, 1169, 1092, 690; ^1H NMR (CD_3OD) δ 7.82 (2H, d, J = 7.8), 7.57 (3H, m), 4.74 (1H, m), 4.47 (1H, m), 4.24-4.10 (2H, m), 3.72-3.47 (4H, m), 2.62-2.48 (3H, m), 2.20 (1H, m), 1.94-1.35 (3H, m). MS (ES^+) 480 (M^+ - 1, 100%). Accurate mass calculated for $C_{19}H_{24}SN_5O_8$ (MH^+): 482.1346. Found: 482.1325.

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1056), was prepared by the method used for **265** (95%): mp. >300°C; IR (KBr) 3392, 1660, 1610, 1507, 1442, 1280, 1171, 1149, 1133. ^1H NMR (CD_3OD) δ 7.74 (2H, d J = 8.7), 6.84 (2H, d J = 8.7) 4.58 (1H, m), 4.41 (1H, bd, J = 12.6), 4.28 (1H, m), 3.85 (3H, m), 2.98 (1H, m), 2.8-2.3 (3H, m), 2.3-1.6 (4H, m).

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1015), was prepared by a similar method as used for **265** to afford a white solid (142mg, 58%): mp. 170-5°C; $[\alpha]_D^{25}$ +32.7° (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 3325, 2969, 1784, 1662, 1485, 1440, 1292, 1258, 1037; ^{1}H NMR (CD_3OD) δ 7.45 (1H, dd), 7.32 (1H, d), 6.90 (1H, d), 6.05 (2H, s), 5.10-4.90 (1H, m), 4.62-4.54 (1H, m), 4.45-4.35 (1H, m), 4.33-4.22 (1H, m), 3.95-3.65 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.20-1.50 (4H, m).

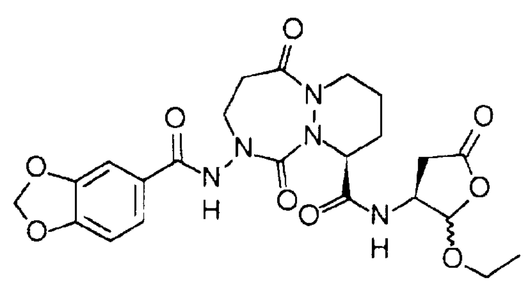


526 **1053**

[3*S*(4*S*)] t-Butyl 3-[7-(benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine]-4-oxobutanoate semicarbazone (526), was prepared by a similar method as used for **502** to afford a glassy solid: $[\alpha]_D^{20}$ +34° (c 0.13, CH_2Cl_2); IR (KBr) 3437, 2929, 1670, 1530, 1428, 1288, 1156; ^{1}H NMR ($CDCl_3$) δ 10.0 (1H, bs), 9.74 (1H, bs), 7.93 (1H, s), 7.80-7.60 (2H, m), 7.40-7.18 (3H, m), 6.15-5.30 (2H, bs), 5.00-4.85 (2H, m), 4.50-4.25 (1H, m), 3.95-3.75 (3H, m), 3.12-2.78 (2H, m), 2.73-1.60 (7H, m), 1.36 (9H, s). Anal. Calcd for

$C_{27}H_{34}N_8O_7S$: C, 52.76; H, 5.58; N, 18.23. Found: C, 52.25; H, 5.74; N, 16.30. MS (ES^+) 615.

[3*S*(4*S*)] 3-[7-(Benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1053), was prepared by a similar method as used for **214** to afford a white solid (106mg, 73%): $[\alpha]_D^{20}$ +22° (c 0.10, MeOH); IR (KBr) 3428, 2944, 1733, 1652, 1532, 1433, 1337, 1288, 1186; ^{1}H NMR (CD_3OD) δ 7.95 (1H, s), 7.90-7.85 (2H, m), 7.43-7.35 (2H, m), 4.98 (1H, m), 4.65-4.52 (1H, m), 4.40-4.20 (2H, m), 3.85-3.70 (3H, m), 3.30-3.25 (3H, m), 3.03-2.85 (1H, m), 2.70-2.31 (3H, m), 2.10-1.55 (4H, m). MS (ES^+) 500 (as methyl acetal of the aldehyde).



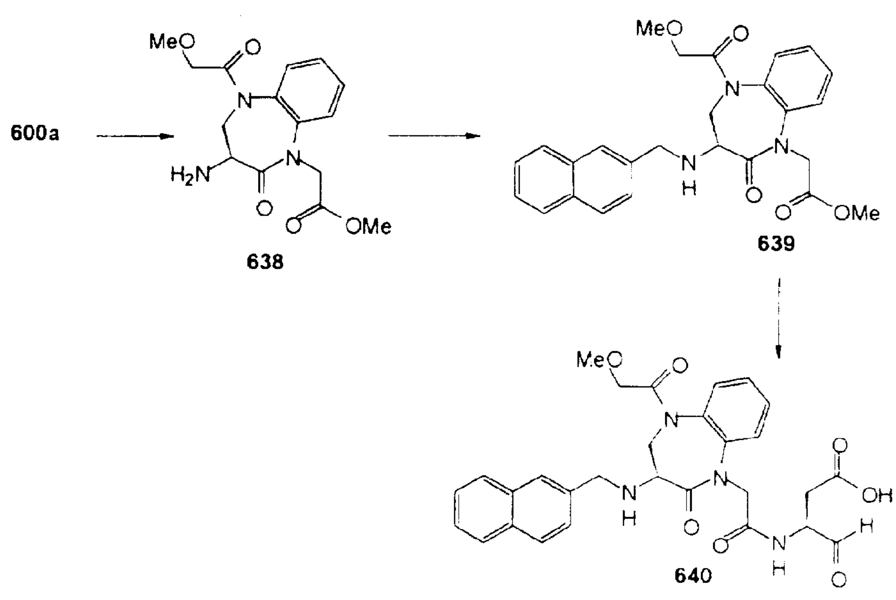
528

[4*S*(2*RS*,3*S*)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (528), was prepared by a similar method as compound **213e** to afford a mixture of diastereomers (Syn: anti isomer ratio 1:1) as a creamy white foamy solid (1.05g,

58%): mp. 124-32°C; IR (KBr) 3312, 2979, 1790, 1664, 1610, 1532, 1485, 1285, 1120, 1037, 932; ^{1}H NMR (D_6-DMSO) δ 10.39 (1H, s), 8.71 (0.5H, d), 8.43 (0.5H, d), 7.45 (1H, d), 7.36 (1H, s), 7.04 (1H, d), 6.12 (2H, s), 5.58 (0.5H, d), 5.34 (0.5H, s), 4.95-4.85 (1H, m), 4.70-4.52 (0.5H, m), 4.35-4.10 (1.5H, m), 3.95-3.50 (5H, m), 3.03 (0.5H, dd), 2.90-2.55 (1.5H, m), 2.46-2.20 (2H, m), 2.10-2.40 (4H, m), 1.16-1.13 (3H, 2 x t). Anal. Calcd for $C_{23}H_{27}N_5O_9 \cdot 0.6H_2O$: C, 52.29; H, 5.38; N, 13.26. Found: C, 52.53; H, 5.35; N, 12.78. MS (ES^+) 519 (M^+ + 2, 27%), 518 (M^+ + 1, 100), 472 (7), 374 (12), 373 (53), 345 (14), 149 (12).

Example 31

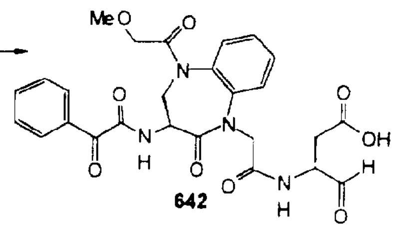
Compounds **640**, **642**, **645**, **650**, **653**, **655**, **656**, **662**, **668**, **669**, **670**, **671**, **677**, **678**, **681**, **682**, **683**, **684**, **686**, **688a**, **688b**, **6891**, **689b**, **690a**, **690b**, **691a**, **691b**, **695a**, **695b**, **695c**, **692a**, **692b**, **693** and **694** were prepared as follows.



(3*S*)-2-Oxo-3-amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (638), was synthesized from **600a** by methods similar to those used for making **602m** from **600a** to afford 2.4g of **638** as a white solid.

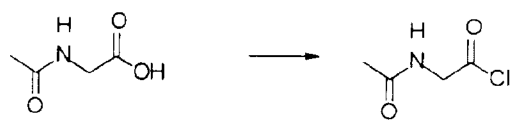
(3*S*)-2-Oxo-3-(2-naphthylmethylene)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (639). To a solution of **638** (630 mg, 1.76 mmol) and 2-naphthylmethyl bromide (428 mg, 1.94 mmol) in CH_3CN was added K_2CO_3 (608 mg, 4.4 mmol). The resulting mixture was stirred at ambient temperature. After 18 hours, the reaction mixture was diluted with CH_2Cl_2, washed with water then brine, dried over Na_2SO_4 then concentrated in vacuo. Flash chromatography (SiO_2, 0 to 20% EtOAc/CH_2Cl_2) afforded 450mg of **639**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(2-naphthylmethylene)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (640), was synthesized by methods used to make **605v** from **602v** to afford 205 mg of **640** as a white solid, ^1H NMR ($CDCl_3$) δ 2.4-2.55(m, 1H), 2.65-2.8(m, 1H), 3.2(s, 3H), 3.72-3.78(m, 1H), 3.85-4.0(m, 2H), 4.22-4.28(d, 1H), 4.26-4.5(m, 4H), 4.58-4.75(m, 1H), 4.78-4.85(m, 1H), 5.0-5.08(t, 1H), 7.35-7.65(m, 7H), 7.85-8.02(m, 4H).

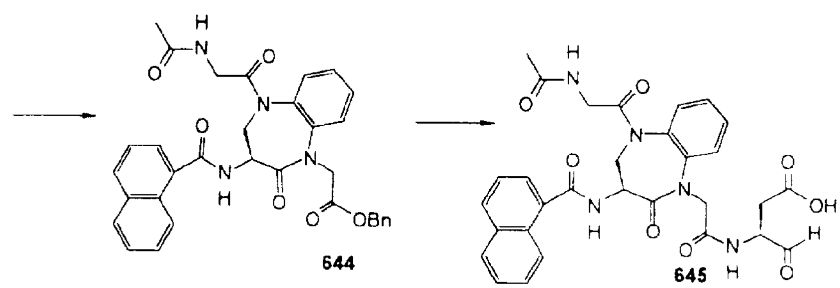


638 → 642

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylformylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (642), was synthesized from **638** by similar methods used to make **605m** to afford 213 mg of **642**, ^{1}H NMR (CD_3OD) δ 2.5(m, 1H), 2.68(ddd, 1H), 3.25(s, 2H), 3.3(s, 3H), 3.78(m, 2H), 4.0(d, 1H), 4.3(m, 1H), 4.6(m, 2H), 4.85(br. s, 2H), 7.08-7.22(m, 2H), 7.35(m, 1H), 7.4-7.65(m, 4H), 7.7(dd, 1H), 8.1(dd, 1H).



643



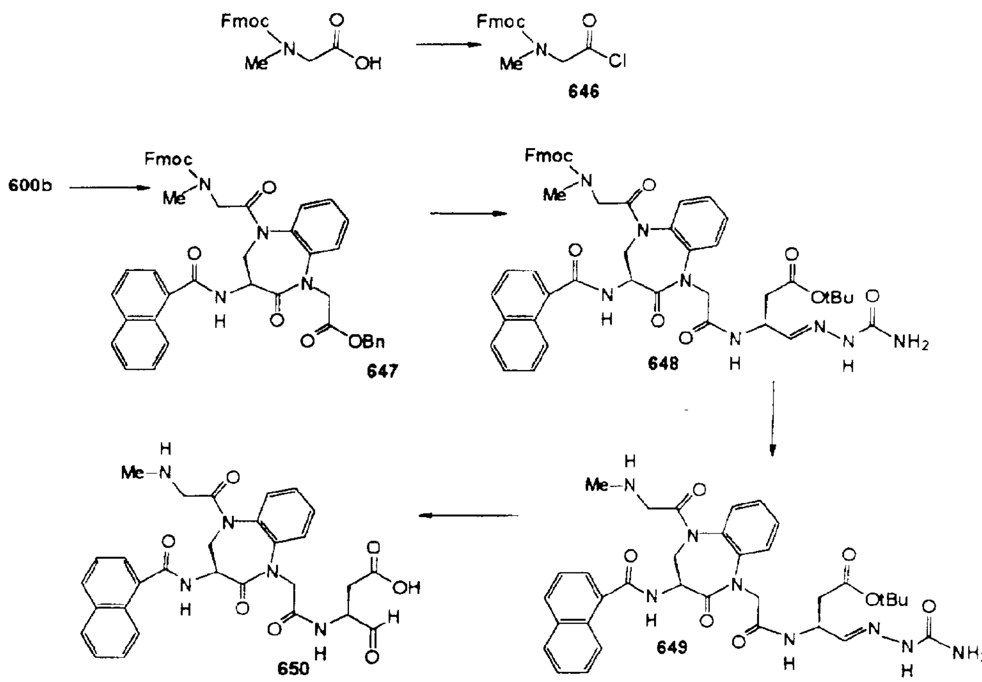
600b → 644 → 645

2-Acetamido-acetyl chloride (643). To a suspension of N-acetyl glycine (200 mg, 1.7 mmol) in CH_2Cl_2 (2.5 mLs) containing DMF (0.005 mLs) was added oxalyl chloride

(0.450 mLs, 5.1 mmol). After stirring 30 minutes at ambient temperature, the mixture was concentrated to afford **643** as a crude product.

(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-(2-acetamido)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (644), was synthesized from **600b** by methods used to make **602d** from **600b** using **643** to afford 112 mg of **644**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-(2-acetamido)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (645), was synthesized from **644** by methods used to make **605d** from **602d** to afford 43 mg of **645** as a white solid, ^{1}H NMR (CD_3OD) δ 1.95(s, 3H), 2.4(m, 1H), 2.65(m, 1H), 3.4(s, 1H), 3.55(m, 1H), 3.85(m, 1H), 4.05(d, 1H), 4.3(m, 1H), 4.4-4.6(m, 2H), 5.0(m, 1H), 7.4-7.7(m, 6H), 7.85-8.0(m, 2H).



2-(*N*-Methyl, *N*-fluorenylmethoxycarbonyl)aminoacetyl chloride (646), was prepared from *N*-Fmoc-sarcosine by method used to make **643** to afford **646** as a crude product.

(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-[2-(*N*-methyl, *N*-fluorenylmethoxycarbonyl) amino]acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (647), was synthesized from **600b** by methods used to synthesize **602d** from **600b**, using **646** to afford 481 mg of **647**.

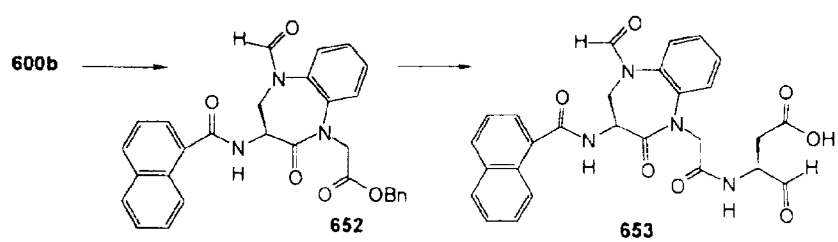
(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-[2-(*N*-methyl, *N*-fluorenylmethoxycarbonyl)amino]acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (648), was

synthesized from **647** by methods used to prepare **604d** from **602d** to afford 409 mg of **648**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-(2-methyl amino) acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (649).

A solution of **648** (409 mg, 0.465 mmol) in MeCN:Et_2NH (4:1, v/v) was stirred at ambient temperature. After 45 minutes, the reaction mixture was concentrated *in vacuo*. Flash chromatography (SiO_2, 5% to 20% MeOH in CH_2Cl_2) afforded 241 mg of **649**.

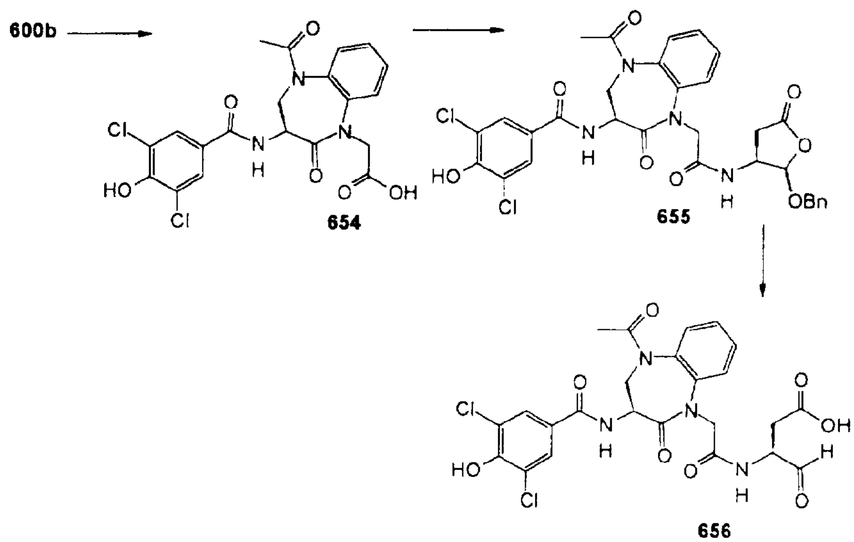
(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-(2-methyl amino) acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (650), was synthesized from **649** by methods used to prepare **605d** from **604** to afford 179 mg of **650** as a white solid, ^1H NMR (CD_3OD) δ 2.4-2.6(m, 2H), 2.7(s, 3H), 3.5(q, 1H), 3.8(m, 2H), 4.2-4.4(m, 2H), 4.3-4.45(m, 1H), 5.0-5.1(m, 2H), 7.4-7.7(m, 6H), 7.85-7.9(m, 2H), 8.2(m, 1H).



(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-formyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (652), was synthesized from **600b** by methods similar to those used to make **602n** from **600b**, using the

reagent obtained from reacting DMF with 3 equiv. of oxalyl chloride in a CH_2Cl_2 solution as R^3X, to afford 404 mg of **652**.

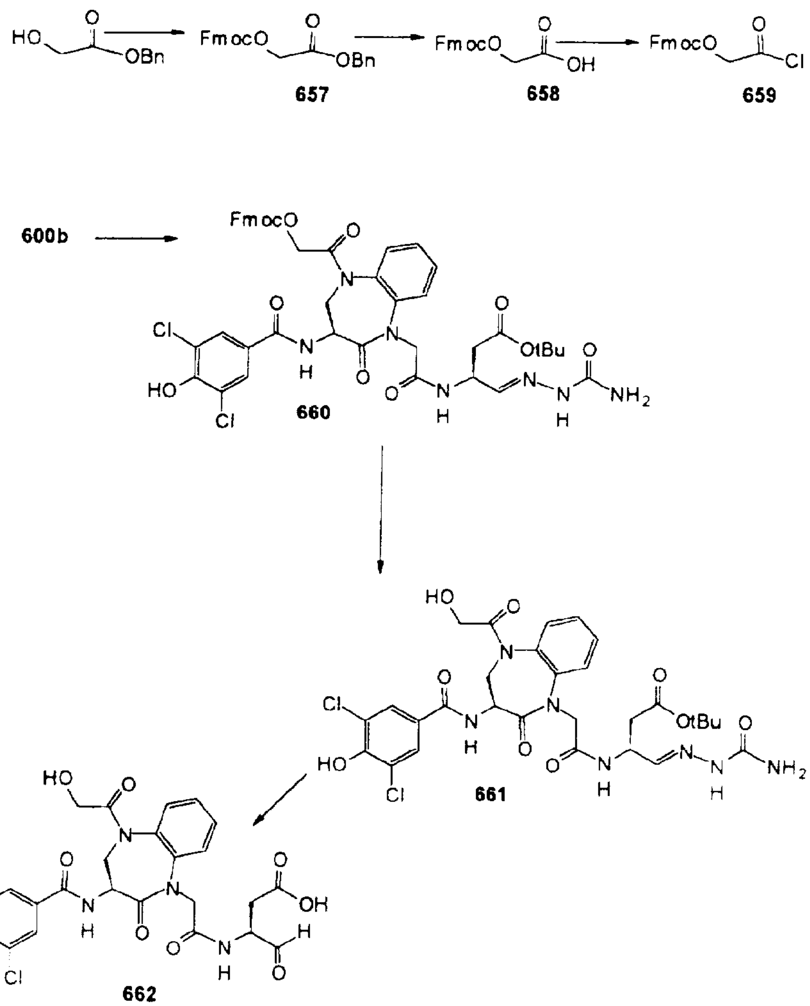
(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (653), was synthesized from **652** by methods used to prepare **605d** from **602d** to afford 84 mg of **653** as a white solid, ^{1}H NMR (CD_3OD) δ 2.3(m, 1H), 2.55(dd, 1H), 3.75(br. s, 1H), 4.25-4.6(m 5H), 5.15(m, 1H), 7.2-7.45(m, 6H), 7.8-7.9(dd, 3H), 8.1(s, 1H), 8.2(m, 2H).



(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (654), was synthesized from **600b** using methods similar to those used for preparing **603d** from **600b** to afford 775 mg of **654**.

(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (655), was synthesized from **654** using the method used to prepare **213e** to afford 304 mg of **655**, ^{1}H NMR (CD_3OD) δ 2.4(d, 1H), 2.6-2.75(m, 2H), 3.0(m, 1H), 3.45(m, 1H), 3.8(d, 1H), 4.0(t, 2H), 4.4(m, 2H), 4.5-4.55(m, 2H), 7.2-7.45(m, 4H), 7.85(s, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro, 4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (656), was synthesized from **655** using a method similar to that used to prepare **2002** from **2001** to afford 136 mg of **656** as a white solid, ^{1}H NMR (CD_3OD) δ 1.85(s, 3H), 2.5(m, 1H), 2.65(m, 1H), 3.7(m, 1H), 4.3(m, 1H), 4.55(m, 2H), 7.4-7.6(m, 4H), 7.85(s, 2H).


HO
OBn
FmocO
OBn
657
FmocO
OH
658
FmocO
Cl
659
600b
FmocO
Cl
HO
OtBu
NH2
660
HO
Cl
HO
OtBu
NH2
661
HO
Cl
HO
OH
662

2-(Fluorenylmethoxycarbonyl)hydroxyacetic acid benzyl ester (657). To a solution of benzyl glycolate (6.0 g, 36.1 mmol) in CH_2Cl_2, cooled via ice-water bath, was added fluorenylmethoxy chloroformate (14 g, 1.5 equiv.) then diisopropylethylamine (9 mLs, 1.5 equiv.). After 1 hour, reaction mixture was poured into a saturated aqueaous solution of ammonium chloride and extracted with CH_2Cl_2, dried over Na_2SO_4 then concentrated *in vacuo*. The product was triturated from MeOH to obtain 2.2 g of **657** as a first crop of white solid.

2-(Fluorenylmethoxycarbonate) acetic acid (658). To a solution of **657** (2.2 g, 5.93 mmol) in tetrahydrofuran was added 5% Pd/C (220 mg). The resulting suspension was vigorously stirred under hydrogen atmosphere. After 90 min, the reaction mixture was filterred through Celite. The filtrate was poured into saturated aqueous $NaHCO_3$ and washed twice with EtOAc. The aqueous layer was then acidified and the product extracted twice with CH_2Cl_2, dried over Na_2SO_4 and concentrated *in vacuo* to afford 1.46 g (88%) of **658** as a white solid.

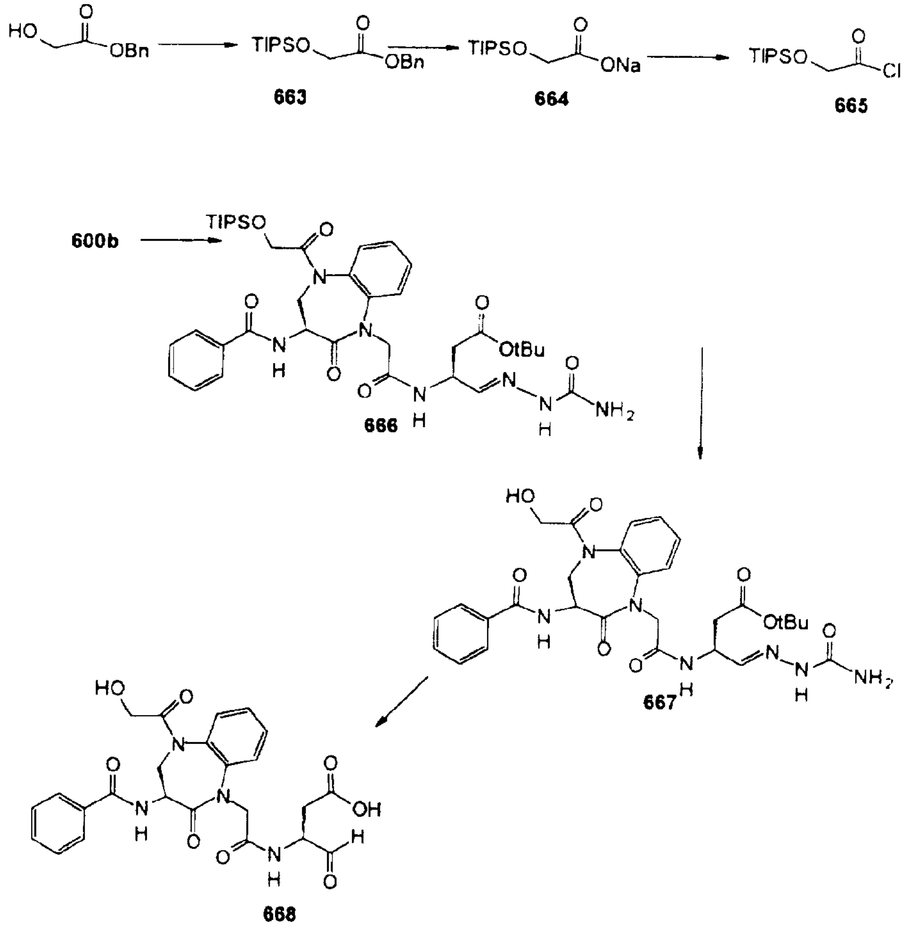
2-(Fluorenylmethoxycarbonate) acetyl chloride (659), was prepared from **658** by the method used to prepare **643** to afford **659** as a crude product.

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-fluorenylmethoxycarbonate)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (660), was synthesized

from **600b**, using **659**, by methods used to prepare **604d** from **600b** to afford 453 mg of **660**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (661). A solution of **660** (423 mg) in MeOH:Et_2NH (1:1, v/v) was stirred at ambient temperature. After 10 minutes, the reaction mixture was concentrated *in vacuo* to a small volume. Precipitation by the addition of ether afforded 230 mg of **661**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-hydroxy) acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (662), was synthesized from **661** by the methods used to prepare **605d** from **604** to afford 37 mg of **662** as a white solid, ^{1}H NMR (CD_3OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.75(m, 1H), 3.9(d, 1H), 4.15(d, 1H), 4.35(m, 1H), 4.5(t, 2H), 4.7(dd, 1H), 7.4-7.6(m, 4H), 7.85(s, 2H).


663
664
665
600b
666
667
668

2-(Triisopropylsilyloxy)acetic acid benzyl ester (663). To a solution of benzyl glycolate (46.91g, 0.282 mol) and diisopropylethylamine (74 mLs, 0.423 mol) in CH_2Cl_2, cooled via water bath, was added a solution of TIPSOTf (95 g, 0.31 mol) in CH_2Cl_2. The resulting mixture was allowed to warm to ambient temperature then poured into water, washed twice with 10% aqueous $NaHSO_4$, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (SiO_2, 0 to 5% EtOAc in hexanes) afforded 71.6 g of **663.**

2-(Triisopropylsilyloxy)acetic acid (664). To a solution of **663** (0.4 g, 1.2 mmol) in EtOAc was added 10% Pd/C (33 mg). The resulting suspension was stirred under hydrogen atmosphere. After 15 hours, the reaction mixture was filterred through Celite and the filtrate concentrated *in vacuo* to afford 0.29 g of an oil. To a solution of this oil in 1,4-dioxane was added $NaHCO_3$ (0.5M, 2.4 mLs). The resulting solution was concentrated *in vacuo* from toluene to afford **664** as a waxy solid.

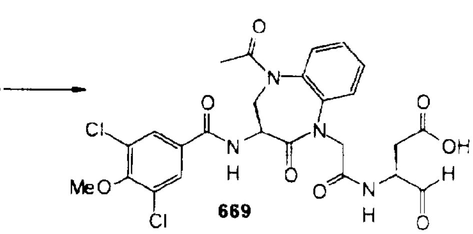
2-(Triisopropylsilyloxy)acetyl chloride (665), was synthesized from **664** by a method similar that used to prepare **643** to afford **665** as a crude product.

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (666), was synthesized from **600b,** using **665,** by methods used to prepare **604d** from **600b** to afford 131 mg of **666.**

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (667). To a solution of **666** (131 mg, 0.17 mmol) in tetrahydrofuran, cooled via ice-water bath, was added tetrabutylammonium fluoride (1M, 0.190 mL). After 2 hours the reaction mixture was poured into water, extracted twice with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo* to afford 63 mg of **667** as a white solid.

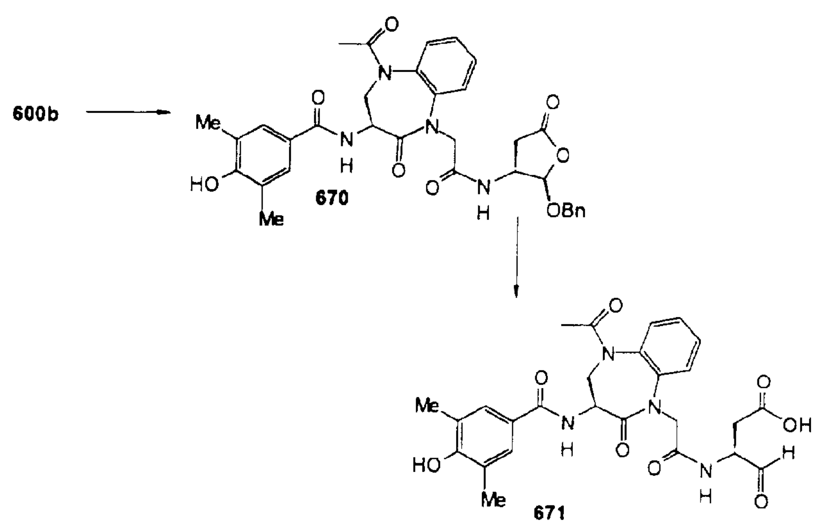
(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(2-hydroxy) acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (668), was synthesized from **667** by the methods used to prepare **605d** from **604d** to afford 48 mg of **668** as a white solid, ^{1}H NMR (CD_3OD) δ 2.45(m, 1H), 2.67(dddd, 1H), 3.78(d, 1H), 3.85(br. m, 1H), 4.05(d, 1H), 4.28(m, 1H), 4.5(m, 2H), 4.65(m, 1H), 4.95(br. s, 2H), 7.4-7.5(m, 4H), 7.52-7.65(m, 3H), 7.88(d, 2H).

600b



(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro-4-methoxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (669), was synthesized from **600b** by the methods used to prepare **605d** from **600b** to afford 63 mg of **669** as a

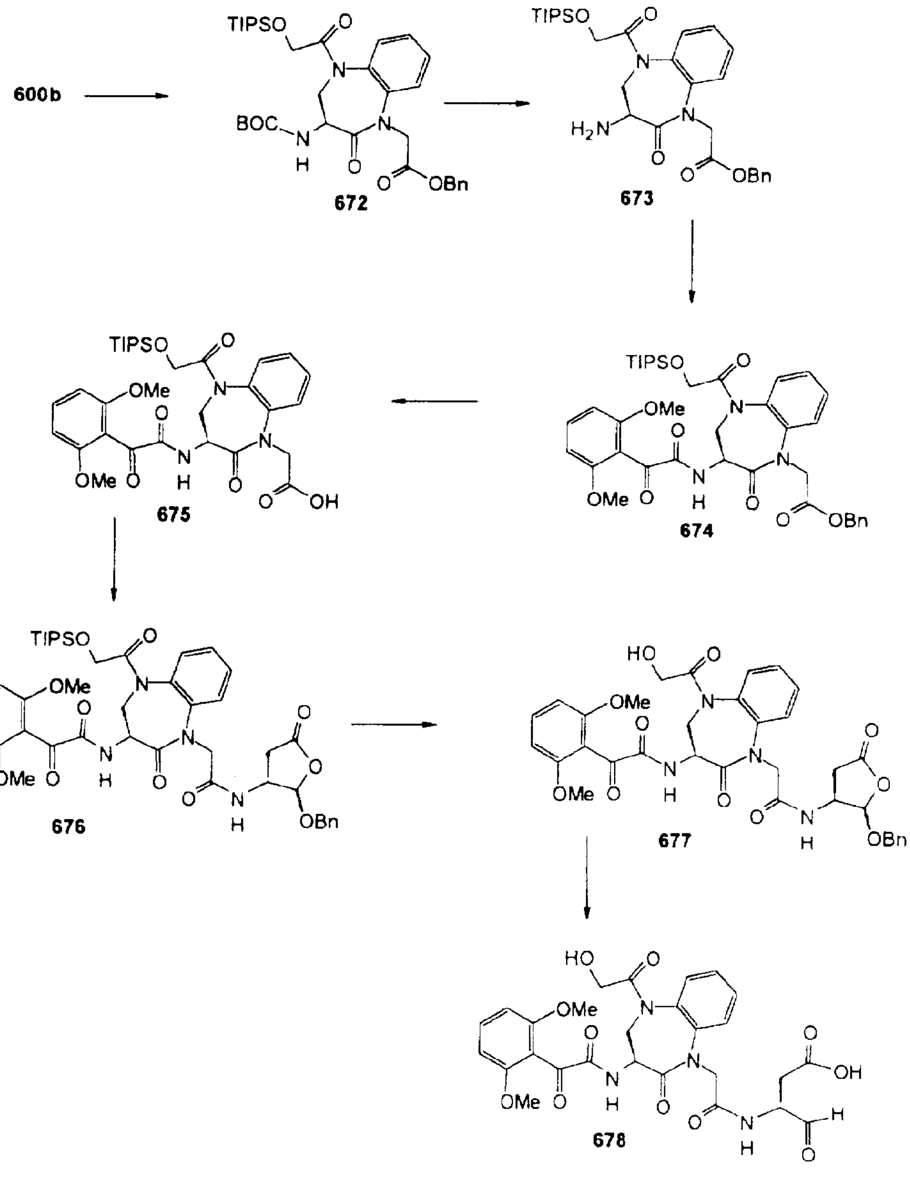
white solid, ^1H NMR (CD_3OD) δ 1.9(s, 3H), 2.4-2.7(m, 2H), 3.6-3.7(m, 2H), 3.9(s, 3H), 4.2-4.4(m, 2H), 4.4-4.6(m, 3H), 7.4-7.8(m, 4H), 7.9(s, 2H).



(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (670), was synthesized from **600b** by the methods used to prepare **655** from **600b** to afford 218 mg of **670** as a white solid, ^1H NMR (CD_3OD) δ 1.7, 1.75(2s, 3H), 2.15, 2.2(2s, 6H), 2.4-2.5(m, 1H), 2.6-2.75(m, 1H), 3.65-3.75(m, 2H), 4.2-4.3(m, 2H), 4.45-4.6(m, 3H), 7.35-7.6(m, 4H), 7.5(s, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (671), was synthesized from **670** by the methods used to prepare **2002** from **2001** to afford 253 mg of **671** as a white solid, ^1H NMR (CD_3OD) δ 1.9(s, 3H), 2.25(s, 6H),

2.4-2.5(m, 1H), 2.6-2.75(m, 1H), 3.65-3.75(m, 2H), 4.2-4.3(m, 2H), 4.45-4.6(m, 3H), 7.35-7.6(m, 4H), 7.5(s, 2H).



(3*S*)-2-Oxo-3-*tert*-butoxycarbonylamino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (672), was synthesized from **600b** by method 1 used to prepare **602n** from **600b** using **665** to afford 1.08 g of **672**.

(3*S*)-2-Oxo-3-amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (673). To a solution of **672** (1.08 g, 1.69 mmol) in CH_2Cl_2 was added 2,6-lutadine (0.8 mL) then TMSOTf (1 mL, 5.1 mmol). After 1 hour, the reaction mixture was poured into $NaHCO_3$ and extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo* to a small volume that was used directly for the next reaction.

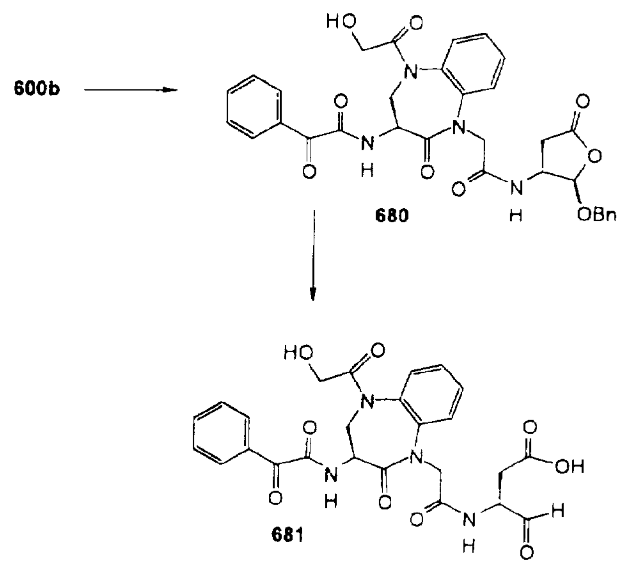
(3*S*)-2-Oxo-3-(1,6-dimethoxybenzoyl formyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (674), was synthesized from **673** by the method used to prepare **602b** to afford 0.91 g of **674**.

(3*S*)-2-Oxo-3-(1,6-dimethoxybenzoyl formyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (675). A solution of **674** (0.365 g, 0.5 mmol) in MeOH was stirred with 1N NaOH (1.2 mL, 1.2 mmol). After 16 hours the reaction mixture was concentrated *in vacuo* then dissolved in water and washed twice with ether. The aqueous layer was acidified with 1N HCl and the product extracted with EtOAc, dried over $MgSO_4$ and concnetrated *in vacuo* to afford 337 mg of **675** as a solid.

(3*S*)-2-Oxo-3-(1,6-dimethoxybenzoylformyl)amino-5-(2-triisopropylsilyloxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (676), was synthesized from **675** by the method used to prepare **213e** to afford 166 mg of **676** as a white solid.

(3*S*)-2-Oxo-3-(1,6-dimethoxybenzoylformyl)amino-5-(2-hydroxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (677). A solution of TBAF (6 mL, 3 mmol) in HOAc (0.46 mL, 8 mmol) was added to **676** (0.213 g, 0.256 mmol). After 16 hours the reaction mixture was poured into EtOAc and washed twice with $NaHCO_3$, once with brine then dried over $MgSO_4$ and concnetrated *in vacuo* to afford 139 mg of **677** as a solid, ^1H NMR ($CDCl_3$) δ 2.4(d, 1H), 2.5(dd, 1H), 2.8(dd, 1H), 2.92(dd, 1H), 3.15(m, 2H), 3.55-3.65(m, 2H), 3.72(s, 6H), 3.92(m, 1H), 4.05(m, 1H), 4.3(m, 1H), 4.42(d, 1H), 4.6(dd, 1H), 4.65-4.8(m, 2H), 4.88(d, 1H), 5.55(d, 1H), 6.55(m, 2H), 6.75(d, 1H), 7.25-7.55(m, 8H), 7.75(m, 2H).

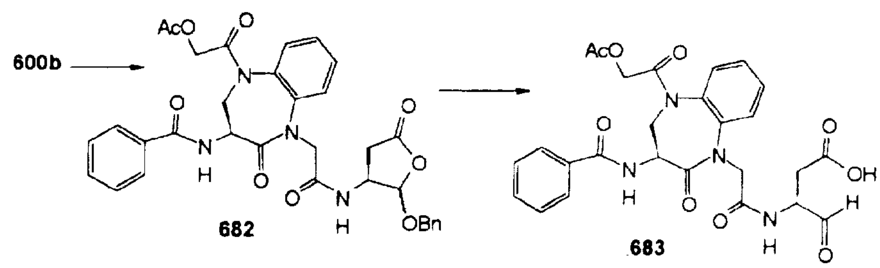
(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethoxybenzoylformyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (678), was synthesized by the method used to prepare **667** from **666** to afford 54 mg of **678** as a white solid, ^1H NMR (CD_3OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.5(m, 2H), 3.75(br. s, 6H), 4.05(d, 1H), 4.3(m, 1H), 4.51-4.6(m, 2H), 4.8(br. m, 2H), 6.7(d, 2H), 7.4-7.5(br. m, 3H), 7.6-7.65(br. m, 2H).



(3*S*)-2-Oxo-3-benzoylformylamino-5-(2-hydroxy)acetyl-N-(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (680), was synthesized from **600b** by the methods used to prepare **677** from **600b** to afford 140 mg of **680** as a white solid, ^{1}H NMR ($CDCl_3$) δ 2.31(d, 1H), 2.4(dd, 2H), 2.75(dd, 2H), 2.85(dd, 1H), 3.36(br. s, 1H), 3.45(br. s, 1H), 3.6(br. t, 2H), 3.82(br. m, 2H), 3.95(br. d, 2H), 4.35(m, 2H), 4.42(d, 1H), 4.55(m, 1H), 4.70(d, 1H), 4.82(br. s, 2H), 5.5(d, 1H), 6.91(d, 1H), 7.25(br. m, 5H), 7.35-7.46(br. m, 3H), 7.5-7.6(m, 2H), 8.15(br. d, 2H).

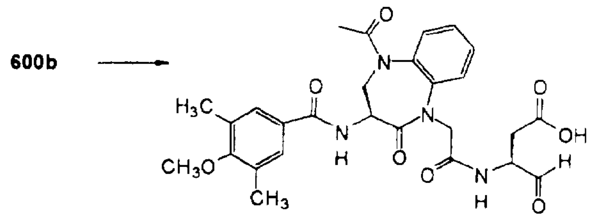
(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylformylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (681), was synthesized from **680** by the method used to prepare **678** from **677** to afford 45 mg of **681** as a grey solid, ^{1}H NMR (CD_3OD) δ 2.5(m, 1H), 2.7(dt, 1H), 3.65-3.85(br. m, 3H), 4.05(m, 1H), 4.3(m, 1H), 4.5-4.7(br. m, 3H),

4.85(br. s, 2H), 7.3(br. m, 2H), 7.4-7.7(m, 5H), 8.15(d, 2H).



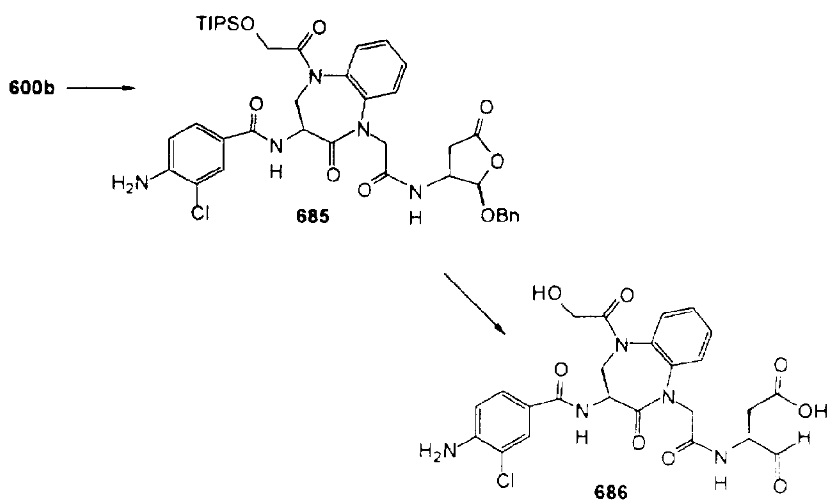
(3*S*)-2-Oxo-3-benzoylamino-5-(2-acetoxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (682), was synthesized from **600b** by the methods used to prepare **655** from **600b** to afford 495 mg of **682** as a white solid, ^{1}H NMR ($CDCl_3$) δ 2.00(s, 3H), 2.05(s, 3H), 2.47(d, 1H), 2.58(dd, 1H), 2.85(dd, 1H), 2.89(dd, 1H), 3.9(m, 2H), 4.05-4.15(m, 2H), 4.19(dd, 1H), 4.45(m, 2H), 4.55-5.05(m, 8H), 5.55(d, 1H), 6.85(d, 1H), 7.15(d, 1H), 7.25-7.55(m, 10H), 7.75(d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(2-acetoxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (683), was synthesized from **682** by the method used to prepare **2002** from **2001** to afford 82 mg of **683** as a white solid, ^{1}H NMR (CD_3OD) δ 2.1(s, 3H), 2.5(m, 1H), 2.68(m, 1H), 3.8(m, 1H), 4.29(dd, 1H), 4.31(m, 1H), 4.45(d, 1H), 4.55(d, 1H), 4.6(d, 1H), 4.72(d, 1H), 4.95(br. s, 2H), 7.45(br. m, 2H), 7.52-7.65(br. m, 5H), 7.88(d, 2H).



684

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (684), was synthesized from **600b** by the method used to prepare **605d** from **600b** to afford 72 mg of **684** as a white solid, ^{1}H NMR (CD_3OD) δ 1.9(s, 3H), 2.25(s, 6H), 2.45(m, 1H), 2.6(m, 1H), 3.3(s, 1H), 3.7(s, 3H), 4.25(m, 1H), 4.45-4.6(m, 3H), 7.4(br. s, 2H), 7.55(br. d, 4H).



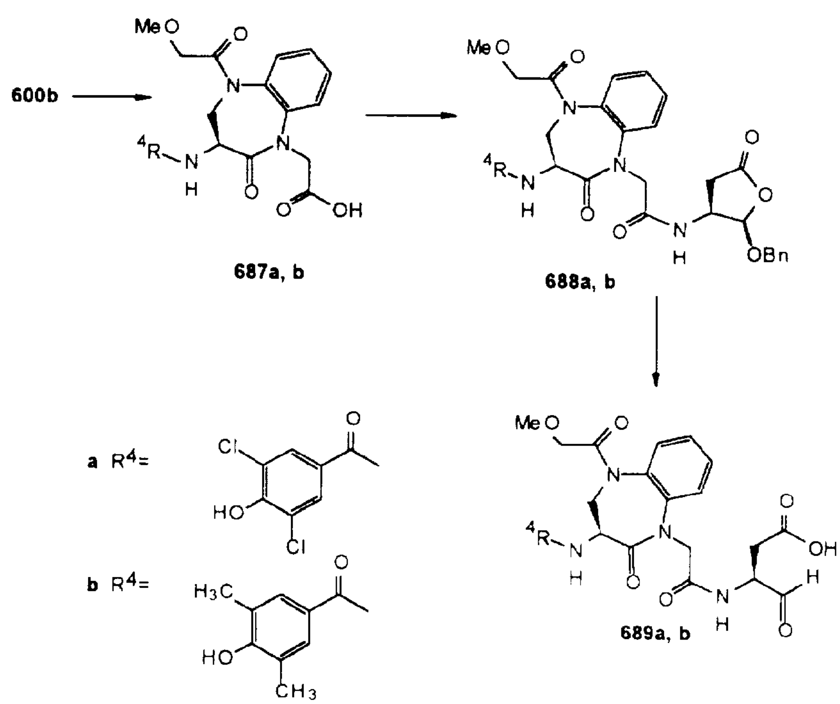
685

686

**(3*S*)-2-Oxo-3-(3-chloro-4-aminobenzoyl)amino-5-(2-triisopropylsilyloxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-

benzodiazepine-1-acetamide (685), was synthesized from **600b** by the methods used to prepare **676** from **600b** to afford 165 mg of **685**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(3-chloro-4-aminobenzoyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (686). To a solution of **685** (165 mg, 0.21 mmol) in THF was added a solution of TBAF (1M, 0.21 mL). The product was isolated by filtration after precipitation from reaction mixture. Reverse phase chromatography (10% to 80% MeCN in water/ 0.1% TFA) afforded 25 mg of **686** as a white solid, ^{1}H NMR (CD_3OD) δ 2.37-2.42 (m), 2.59-2.70 (m), 3.60-3.89 (m), 4.01 (d), 4.20-4.31 (m), 4.42-4.70 (m), 4.80-5.05 (m), 6.79 (d), 7.32-7.65 (m), 7.81 (s).



(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (687a), was synthesized from **600b** using methods similar to those used for preparing **654** from **600b** to afford 1.6 g of **687a**.

(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (687b), was synthesized from **600b** using methods similar to those used for preparing **654** from **600b** to afford 1.1 g of **687b**.

(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (688a). To a solution of (3*S*,2R,S)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Biorg. Med. Chem. Lett., 2, pp. 613-618 (1992)) (1.13 g, 1.2 equiv) in CH_2Cl_2 was added triphenylphosphine (423 mg, 0.5 equiv), dimethylbarbituric acid (1.26 g, 2.5 equiv), and tetrakistriphenylphosphine palladium (0) (373 mg, 0.1 equiv). After 5 minutes the reaction mixture was cooled via ice-bath then added a solution of **687a** in DMF (1.6 g, 1 equiv), HOBT (480 mg, 1.1 equiv), and EDC (681 mg, 1.1 equiv). The resulting mixture was allowed to stir at ambient temperature. After 16 hours the reaction mixture was poured into $NaHSO_4$ and extracted twice with EtOAc. The organic layer was washed with $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (SiO_2, 20% to 100% EtOAc in CH_2Cl_2) afforded 880mg of **688a** as an off-white solid, ^1H

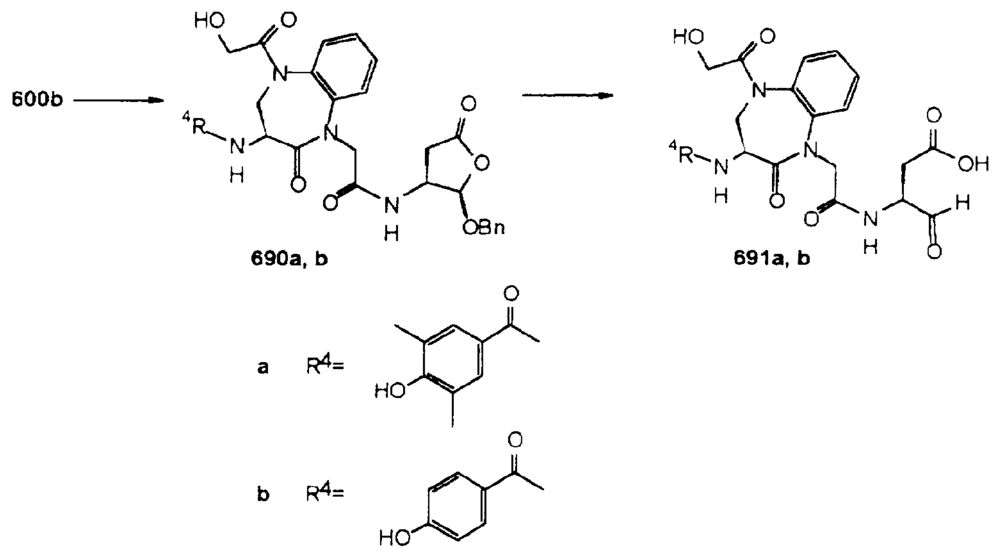
NMR (CD_3OD) δ 2.55(dd, 1H), 2.7(dd, 1H), 3.0(m, 1H), 3.6(m, 1H), 3.75(d, 1H), 3.9-4.0(m, 2H), 4.3-4.45(m, 3H), 4.5-4.6(m, 3H), 4.7(m, 2H), 5.35(s, 1H), 5.55(d, 1H), 7.1-7.5(m, 4H), 7.85(s, 2H).

(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (688b), was synthesized from **687b** by the method used to prepare **688a** from **687a** to afford 960 mg of **688b** as an off-white solid, ^{1}H NMR (CD_3OD) δ 2.6(dd, 1H), 2.7(dd, 1H), 3.0(dd, 1H), 3.2(s, 3H), 3.7(m, 3H), 3.9(m, 2H), 4.4-4.5(m, 2H), 4.6(m, 3H), 5.35(s, 1H), 5.55(d, 1H), 7.25(m, 2H), 7.4-7.5(m, 4H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (689a), was synthesized from **688a** by the method used to prepare **2002** from **2001** to afford 184 mg of **689a** as a white solid, ^{1}H NMR (CD_3OD) δ 2.45(m, 1H), 2.6(m 1H), 3.3(s, 3H), 3.7-3.85(m, 2H), 4.0(d, 1H), 4.3(m, 1H), 4.5-4.6(m, 3H), 7.3-7.6(m, 4H), 7.85(s, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (689b), was synthesized from **688b** by the method used to prepare **2002** from **2001** to afford 412 mg of **689b** as a white solid, ^{1}H NMR (CD_3OD) δ 2.5(m, 1H),

2.7(m, 1H), 3.3(s, 3H), 3.7-3.85(m, 2H), 4.05(dd, 1H), 4.3(m, 1H), 4.6(m, 2H), 7.45-7.4(m, 2H), 7.5(s, 2H), 7.55(m, 2H).



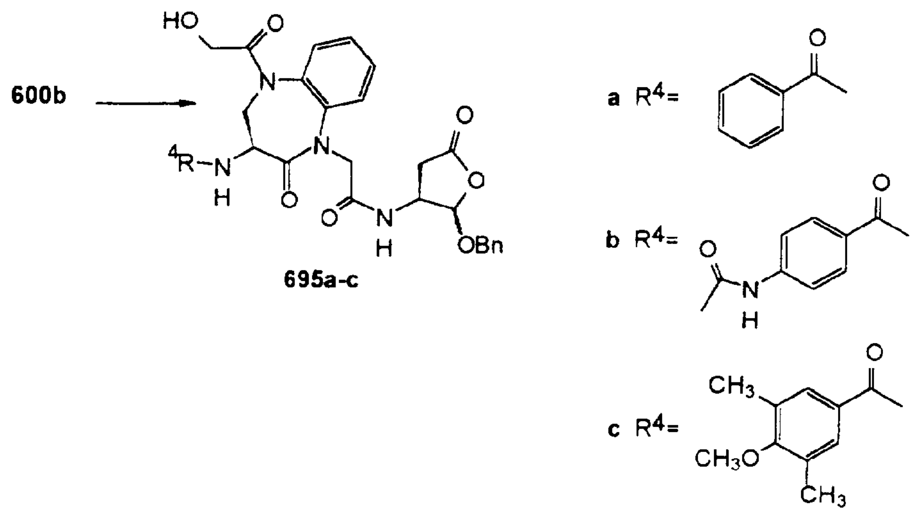
(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (690a), was synthesized from **600b** via methods used to prepare **676** from **600b**, **688a** from **687a**, then **677** from **676** to afford 863 mg of **690a** as a white solid, ^{1}H NMR (CD_3OD) δ 2.2(s, 6H), 2.45(d, 0.5H), 2.6-2.9(m, 1H), 3.05(dd, 0.5H), 3.65-3.85(m, 2H), 3.95-4.1(m, 1H), 4.35-5.0(m, 7H), 5.35(s, 0.5H), 5.65(d, 0.5H), 7.2-7.4(m, 4H), 7.4-7.7(m, 7H).

(3*S*)-2-Oxo-3-(4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (690b), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 200 mg of **690b**, ^{1}H NMR

(CD_3OD) δ 2.49(d, 1H), 2.65(d, 1H), 2.66(d, 1H), 2.85(d, 1H), 2.87(d, 1H), 3.05(dd, 1H), 3.35(br. s, 1H), 3.72(br. s, 2H), 4.01(m, 2H), 4.45(br. m, 1H), 4.6(m, 1H), 4.7(m, 1H), 4.8(m, 1H), 4.95(br. s, 2H), 5.65(d, 1H), 6.8(d, 2H), 7.2-7.35(br. m, 3H), 7.45(m, 2H), 7.75(d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (691a), was synthesized from **690a** by the method used to prepare **2002** from **2001** to afford 560 mg of **691a** as a white solid, ^{1}H NMR (CD_3OD) δ 2.15(s, 6H), 2.45(m, 1H), 2.65(m, 1H), 3.55(m, 1H), 3.7(d, 1H), 4.0(d, 1H), 4.25(m, 1H), 4.5-4.6(m, 3H), 7.3-7.5(m, 6H).

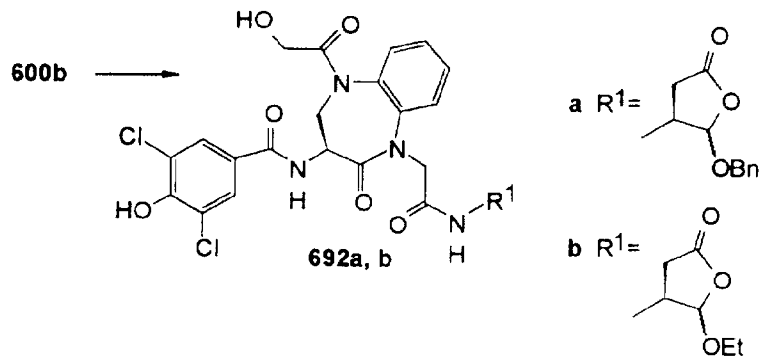
(3*S*)-3-[(3*S*)-2-Oxo-3-(4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (691b), was synthesized from **690b** by the method used to prepare **2002** from **2001** to afford 410 mg of **691b** as a white solid, ^{1}H NMR (CD_3OD) δ 2.5(m, 1H), 2.65(m, 1H), 3.75(m, 1H), 3.8(d, 1H), 4.05(d, 1H), 4.25(m, 1H), 4.5(m, 1H), 4.6(m, 1H), 4.95(br. s, 2H), 6.8(d, 2H), 7.45(m, 2H), 7.6(m, 2H), 7.75(d, 2H).



(3*S*)-2-Oxo-3-benzoylamino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (695a), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 75 mg of **695a**, ^{1}H NMR (CD_3OD) δ 2.2(s, 6H), 2.45(m, 1H), 2.6(m, 1H), 3.65(m, 1H), 3.75(d, 1H), 4.0(d, 1H), 4.28(m, 1H), 4.5(m, 3H), 7.4-7.6(m, 6H).

(3*S*)-2-Oxo-3-(4-acetamidobenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (695b), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 880 mg of **695b**, ^{1}H NMR ($CDCl_3$) δ 2.1(s, 3H), 2.25-2.5(m, 2H), 2.8-2.92(m, 0.5H), 3.15-3.2(m, 0.5H), 3.45-3.6(m, 2H), 3.75-3.95(m, 2H), 4.15-4.25(m, 1H), 4.35-4.6(m, 2H), 4.6-4.88(m, 3H), 5.22(s, 0.25H), 5.33(s, 0.25H), 5.52-5.58(d, 0.5H), 7.15-7.45(m, 9.5H), 7.5-7.75(m, 5H), 8.3-8.35(m, 0.5H), 9.08-9.18(m, 1H).

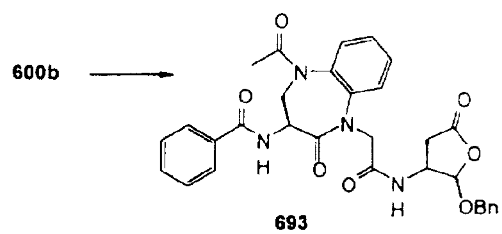
(3*S*)-2*RS*-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-(2-benzyloxy-5-oxo-tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (695c), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 840 mg of **695c**, ^{1}H NMR($CDCl_3$) δ 2.23(s, 3H), 2.26(s, 3H), 2.45-2.62(m, 1H), 2.8-2.9(dd, 0.5H), 2.9-3.05(dd, 0.5H), 3.45-3.63(m, 1H), 3.64(s, 1.5H), 3.68(s, 1.5H), 3.78-4.05(m, 2H), 4.2-4.33(m, 1H), 4.4-4.63(m, 2H), 4.65-4.94(m, 2H), 4.95-5.1(m, 1H), 5.45(s, 0.5H), 5.5-5.6(d, 0.5H), 6.9-6.95(d, 1H), 7.25-7.7(m, 12H).



692a, b

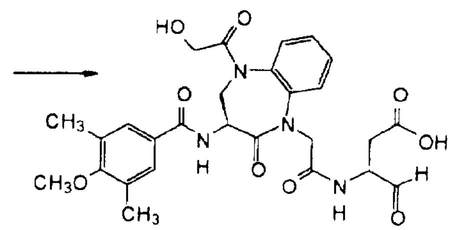
(3*S*)-2-Oxo-3-(3,5-dichloro4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (692a), was synthesized from **600b** via methods used to prepare **661** from **600b**, excluding steps used to make **604d** from **603d**, using instead the method to prepare **688a** from **687a** to afford 854 mg of **692a** , ^{1}H NMR (CD_3OD) δ 2.45(d, 1H), 2.6(m, 1H), 2.7(m, 1H), 3.0(m, 1H), 3.5-3.7(m, 4H), 4.0(q, 2H), 4.45(m, 3H), 4.55(m, 4H), 5.35(s, 1H), 5.6(d, 1H), 7.2-7.5(m, 9H), 7.85(s, 2H).

(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-ethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (692b), was synthesized from **600b** via methods used to prepare **661** from **600b**, excluding steps used to make **604d** from **603d**, using instead the method to prepare **688a** from **687a** to afford 207 mg of **692b** , ^{1}H NMR (CD_3OD) δ 1.05(t, 3H), 1.15(t, 3H), 2.45(d, 1H), 2.55(m, 1H), 2.7(m, 1H), 3.55(m, 2H), 3.6-3.75(m, 5H), 4.0(dd, 2H), 4.3(d, 1H), 4.4-4.7(m, 5H), 5.25(s, 1H), 5.5(d, 1H), 7.25-7.6(m, 4H), 7.85(s, 2H).



693

(3*S*)-2-Oxo-3-benzoylamino-5-acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (693), was synthesized from **600b** via methods used to prepare **688a** from **600b** to afford 30 mg of **693** , ^{1}H NMR (CD_3OD) δ 1.7(s, 3H), 1.8(s, 3H), 2.51(d, 1H), 2.6(m, 1H), 2.85(m, 1H), 3.0(m, 1H), 3.75(br. d, 2H), 4.0-4.1(dd, 2H), 4.5-5.0(m, 6H), 5.45(s, 1H), 5.55(s, 1H), 7.15-7.85(m, 14H).

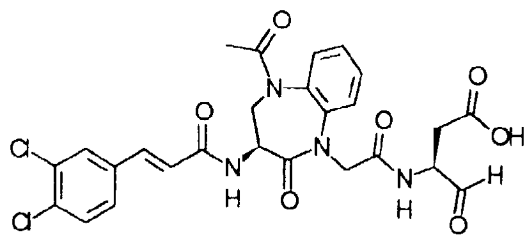
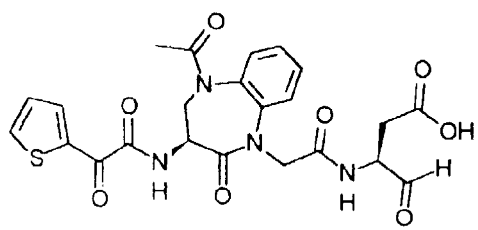
691c

694

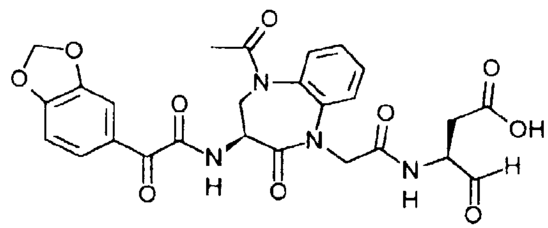
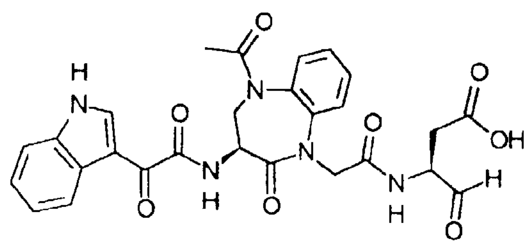
(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (694), was synthesized from **691c** by the method used to prepare **2002** from **2001** to afford 380 mg of **694** as a white solid, ^{1}H NMR (CD_3OD) δ 2.25(s, 6H), 2.45(m, 1H), 2.65(m, 1H), 3.65(m, 5H), 4.0(d, 1H), 4.28(m, 1H), 4.55(d, 2H), 4.95(m, 1H), 7.4-7.6(m, 6H).

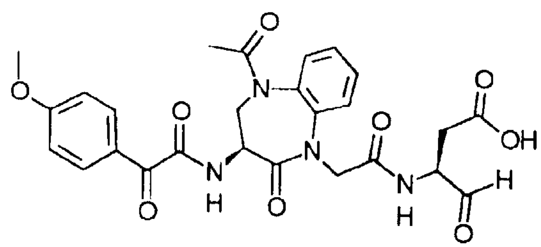
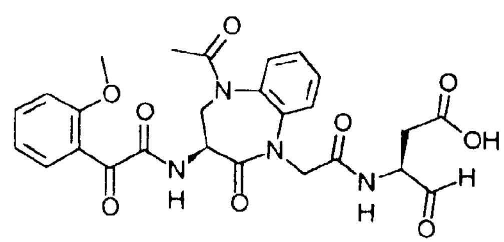
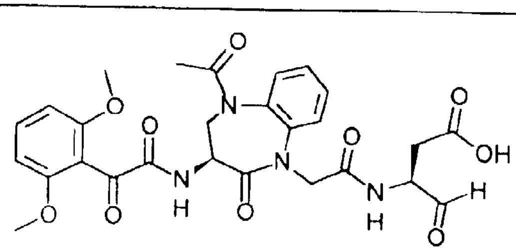
Compounds **700-711** were prepared by methods similar to the methods used to prepare compounds **619-635** (see, Example 13). Physical data for compounds **700-711** is listed in Table 25.

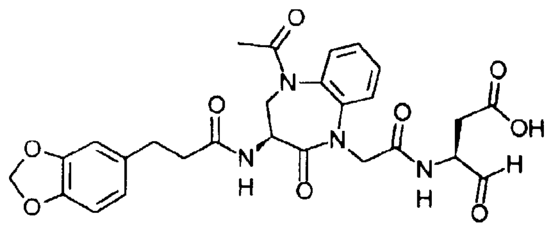
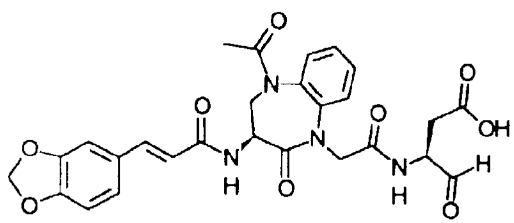
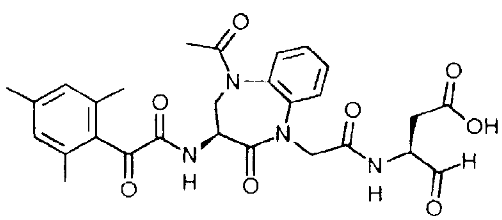
Compounds **910-915** and **918-921** were prepared as described below. Physical data for these compounds is listed in Table 26.

Table 25

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
700		C26H24Cl2N4O7	575.41	14.061 (2) 97%	600
701		C23H22N4O8S	514.52	15.589 (1) 97%	538.8

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
702		C26H24N4O10	552.50	15.855 (1) 98%	575.9
703		C27H25N5O8	547.53	10.315 (2) 97%	572.1

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
704		C26H26N4O9	538.52	10.475 (2) 96%	562.1
705		C26H26N4O9	538.52	14.260 (1) 72%	562.1
706		C27H28N4O10	568.55	14.836 (1) 97%	592.4

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
707		C27H28N4O9	552.55	15.952 (1) 98%	575.9
708		C27H26N4O9	550.53	10.731 (2) 93%	574.6
709		C28H30N4O8	550.57	13.192 (2) 95%	574

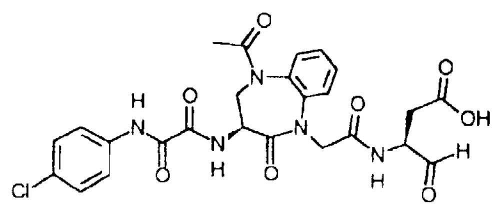
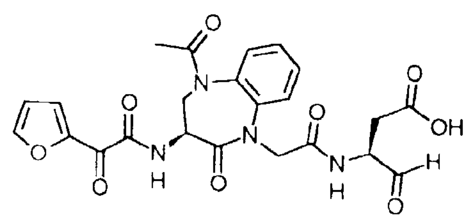
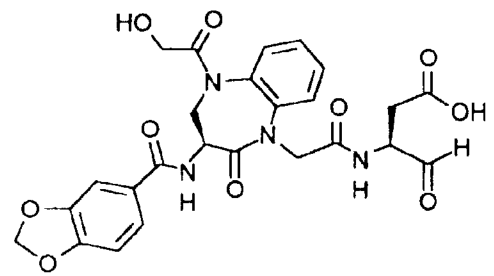
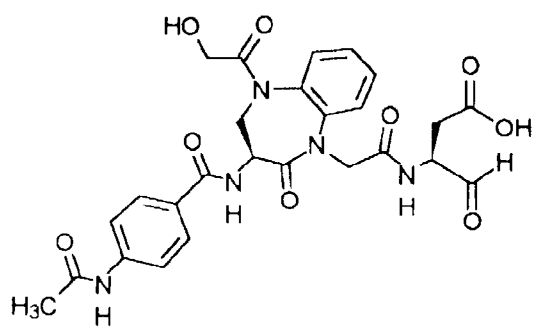
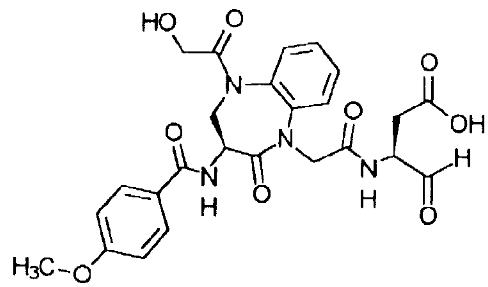
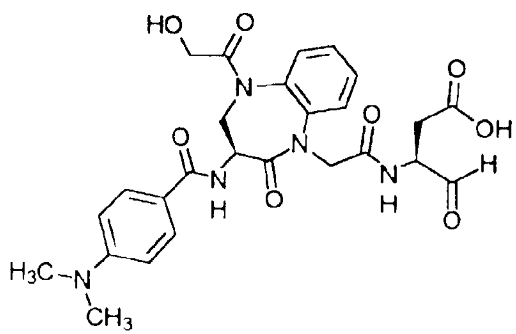
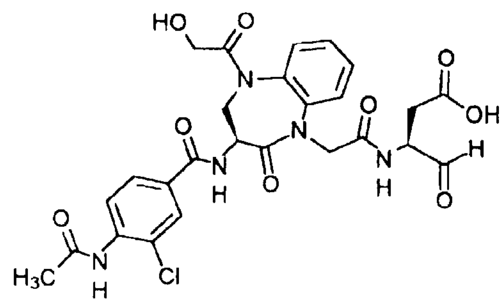
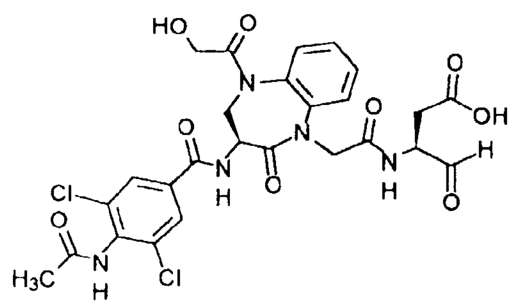
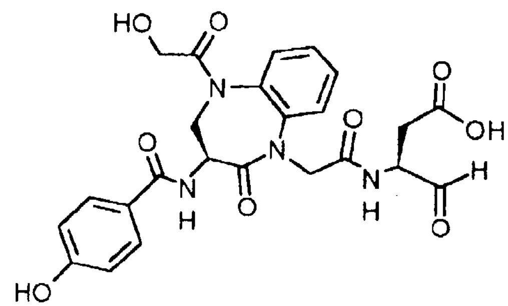
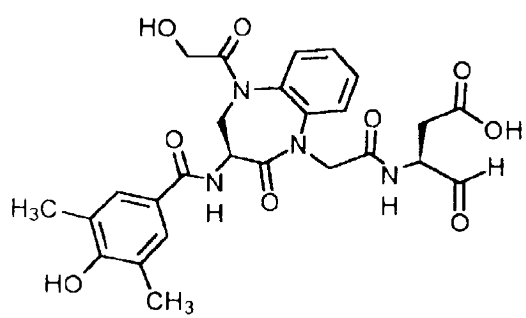
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
710		C25H24ClN5O8	557.95	12.406 (2) 98%	582.2
711		C23H22N4O9	498.45	13.072 (1) 99%	521.9

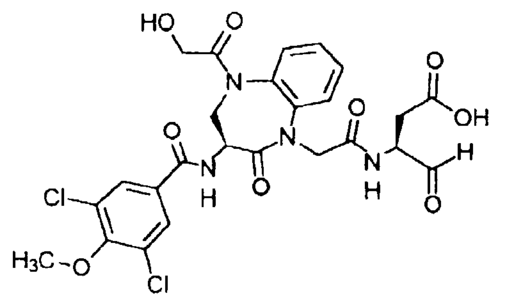
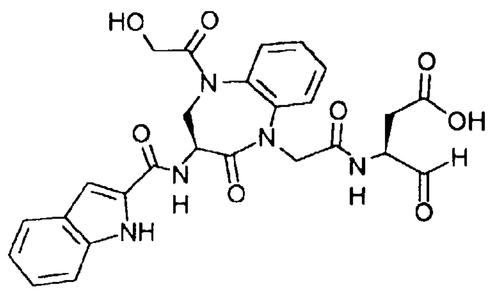
Table 26

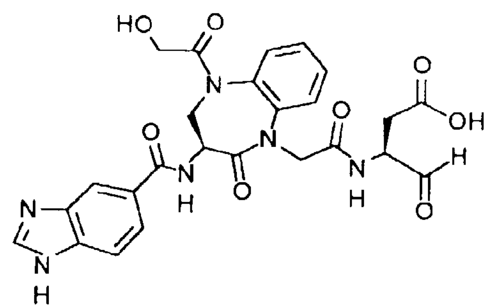
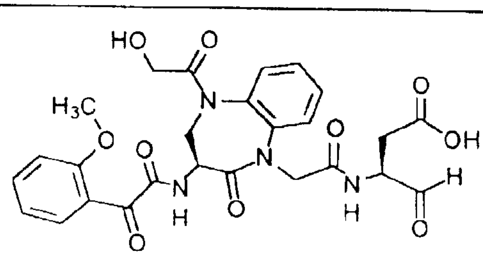
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
910		C25H24N4O10	540.49	8.172 (2) 99%	564.4
911		C26H27N5O9	553.53	6.949 (2) 99%	577.5

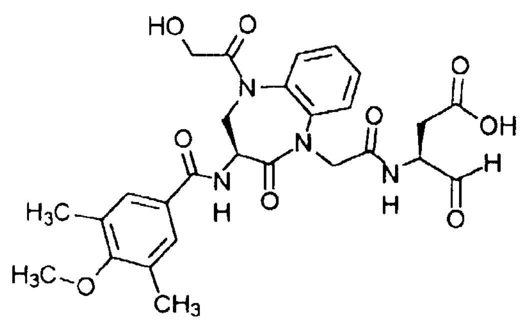
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
912		C25H26N4O9	526.51	8.317 (2) 99%	550.7
913		C26H29N5O8	539.55	6.588 (2) 99%	563.5

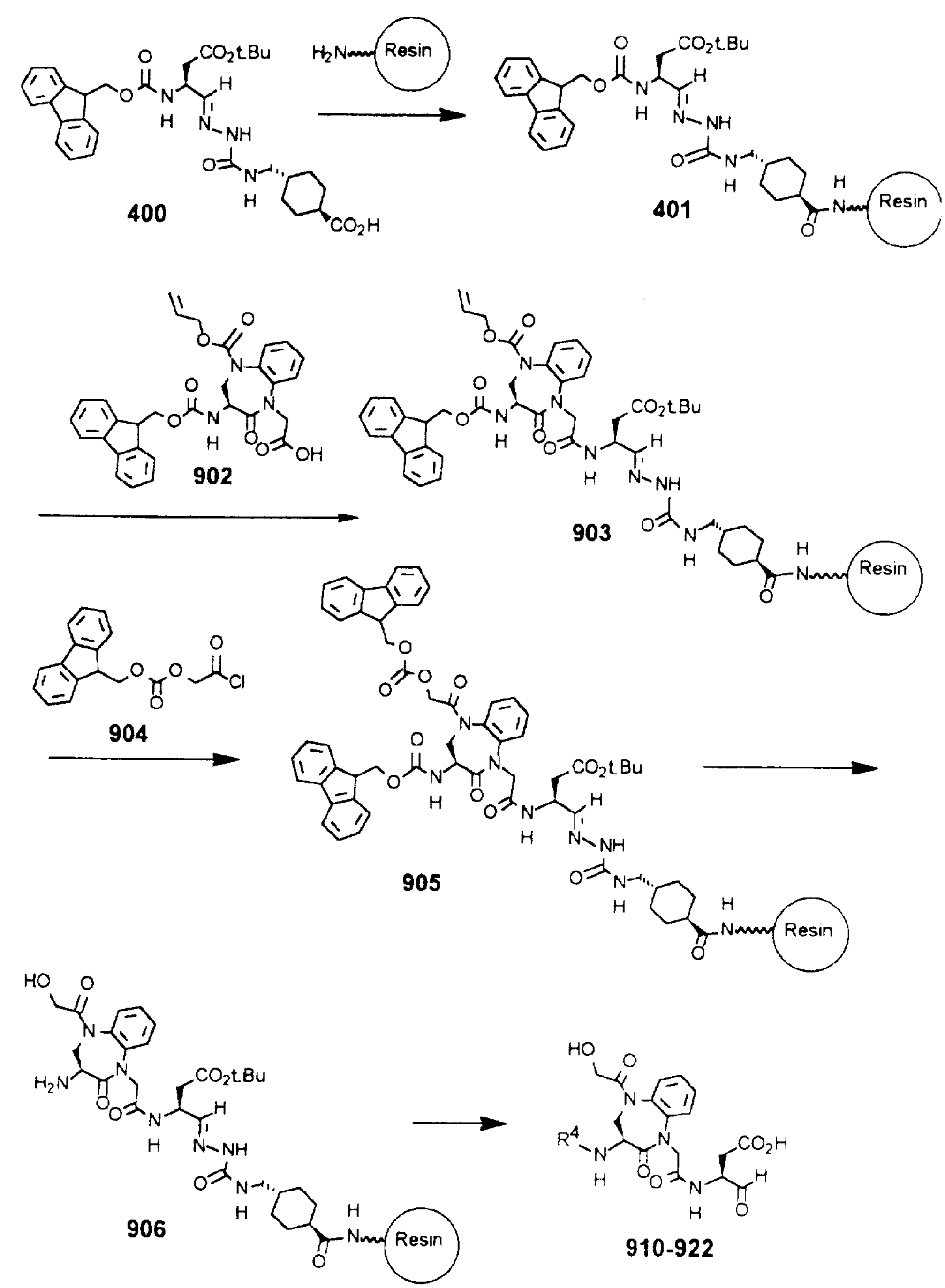
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
914		C26H26ClN5O9	587.98	7.815 (2) 99%	612.2
915		C26H25Cl2N5O9	622.42	7.490 (2) 98%	647

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
916/691b		C24H24N4O9	512.48	6.331 (2) 98%	537
917/691a		C26H28N4O9	540.53	8.114 (2) 99%	564.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
918		C25H24Cl2N4O9	595.40	11.817 (2) 99%	619.3
919		C26H25N5O8	535.52	9.709 (2) 91%	559.7

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
920		C25H24N6O8	536.51	5.494 (2) 98%	560.6
921		C26H26N4O10	554.52	7.827 (2) 96%	579.1

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
922/694		C27H30N4O9	554.56	10.024 (2) 99%	578.8


400
401
902
903
904
905
906
910-922
Resin
CO_2tBu
CO_2H
H_2N
R^4

Step A. Synthesis of 401. TentaGel S® NH_2 resin (0.25 mmol/g, 6.8 g) was placed in a glass shaker vessel and washed with dimethylacetamide (3 X 20 mL). To a solution of **400** (1.70 g, 2.9 mmol, prepared from (3S) 3-(fluorenylmethyloxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)) in dimethylacetamide (15 mL) was added O-benzotriazole-N,N,N,N'-tetramethyluronium hexafluorophosphate (HBTU; 1.09 g, 2.9 mmol), and DIEA (1.0 mL, 5.7 mmol). The solution was added to the resin, followed by dimethylacetamide (5 mL). The reaction mixture was agitated for 3 h at room temperature using a wrist arm shaker. The resin was isolated by suction filtration and washed with dimethylacetamide (6 X 20 mL). A sample of resin (7.4 mg) was thoroughly washed with 50% methanol in dichloromethane and dried under suction. Deprotection of the Fmoc group using 20% piperidine in dimethylacetamide (10.0 mL) and UV analysis of the solution revealed a substitution of 0.19 mmol g^{-1}.

Step B. Synthesis of 903. Resin **401** was deprotected with 20% (v/v) piperidine/dimethylacetamide (20 mL) for 10 min (shaking) and then for 10 min with fresh piperidine reagent (20 ml). The resin was then washed with dimethylacetamide (6 X 20 ml). A solution of **902** (1.52 g, 2.81 mmol) was treated with HBTU (1.07 g, 2.83 mmol) and DIEA (1.0 mL, 5.7 mmol) and transferred to the resin, followed by dimethylacetamide (5 mL). The reaction mixture was agitated for 2.5 h at room temperature using a wrist arm shaker. The resin was isolated by suction filtration and washed with

dimethylacetamide (4 X 20 mL) and dichloromethane (4 X 20 mL), and dried under nitrogen purge. Resin substitution was performed as described for **401** and determined to be 0.169 mmol g^{-1}.

Step C. Synthesis of 905. Resin **903** (7.54 g, 1.27 mmol) and dimedone (2.19 g, 15.6 mmol) were placed in a 100 mL round bottomed flask and freshly distilled anhydrous tetrahydrofuran (60 mL) was added. Tetrakis(triphenylphosphine)palladium (0) (0.32 g, 0.28 mmol) was added and the nitrogen blanketed, sealed reaction was agitated for 15 h on a wrist action shaker. The resin was filtered, washed with dimethylacetamide (4 X 20 mL), dichloromethane (4 X 20 mL) and dimethylacetamide (1 X 20 mL). Sufficient dimethylacetamide was added to the resin to obtain a slurry followed by pyridine (1.5 mL, 18.5 mmol) and a solution of **904** (5.5 mmol) in dichloromethane (10 mL). The reaction was shaken under nitrogen for 8 h, then filtered. The resin was washed with dimethylacetamide (5 X 20 mL) and dichloromethane (5 X 20 mL).

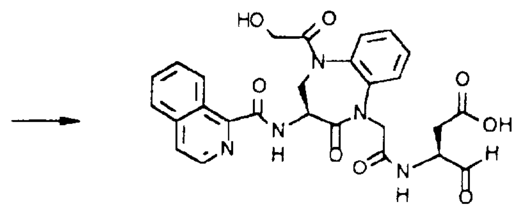
Step D. Synthesis of 906. This compound was prepared from resin **905** (0.24 g, 0.038 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (3 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 10 min followed by fresh reagent (1 mL) for 20 min to yield resin **906**. The resin was washed with dimethylformamide (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL).

Step E. (910-922) Resin **906** was acylated with a solution of 0.4M carboxylic acid and 0.4M HOBT in N-methypyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.25 mL) and the reaction was shaken for 2 hr at room temperature. The resin was washed with N-methylpyrrolidone (1 X 1 mL), dimethylformamide (4 X 1 mL), 50% methanol in dichloromethane (5 X 1 mL) and dried in air. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H_2O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (2 X 1 mL), the combined filtrates were added to cold 1:1 ether:hexane (35 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in acetonitrile (0.5 mL) and H_2O (0.5 mL) and filtered through 0.45 micron microcentrifuge filters. The compound was purified by semi-preparative RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (10% - 50%) containing 0.1% TFA (v/v) over 30 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **910-922**.

Analytical HPLC methods:

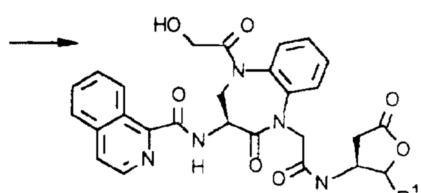
(1) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm). Linear acetonitrile gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

(2) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm). Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

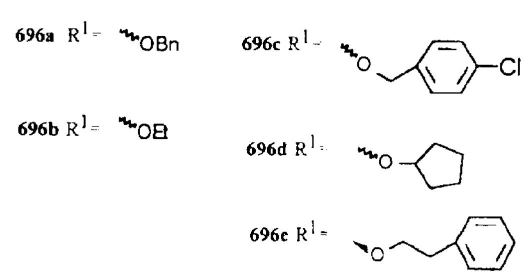
600b 

696

(3*S*)-3-[(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (696) was synthesized from **600b** by the method used to prepare **691a** from **600b** to afford **696**. ^{1}H NMR (CD_3OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.75(d, 1H), 3.95(q, 1H), 4.05(d, 1H), 4.3(m, 1H), 4.45-4.65(m, 2H), 5.05(m, 1H), 7.5-7.6(m, 3H), 7.7(t, 1H), 7.8(t, 1H), 7.98(t, 1H), 8.55(d, 1H), 9.1(d, 1H).

600b 

696a-e



(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (696a) was synthesized from **600b** via methods used to prepare **690a** from **600b** to afford **696a**. ^{1}H NMR ($CDCl_3$) δ 0.95(t, 2H), 1.25(t, 1H), 1.4(m, 2H), 1.55(m, 1H), 2.55(m, 1H), 2.85(m, 1H), 2.95(dd, 1H), 3.15(m, 1H), 3.55(m, 1H), 3.9(m, 2H), 4.35(t, 1H), 4.4-4.55(m, 2H), 4.75(m, 1H), 4.8-5.05(m, 2H), 5.45(s, 1H), 5.55(d, 1H), 6.85(d, 1H), 7.15(d, 1H), 7.2-7.5(m, 5H), 7.6-7.8(m, 3H), 8.45(d, 1H), 9.05(d, 1H), 9.35(d, 1H).

(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-ethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696b) was synthesized from **600b** via methods used to prepare **690a** from **600b** to afford **696b**. ^{1}H NMR ($CDCl_3$) δ 0.9(m, 3H), 1.15(q, 3H), 1.15(m, 1H), 1.65(m, 1H), 2.5(m, 1H), 2.8(m, 1H), 2.95-3.0(m, 2H), 3.6(m, 2H), 3.7-3.85(m, 4H), 4.0(m, 2H), 4.3(m, 1H), 4.55(m, 1H), 4.65(m, 1H), 4.85-4.95(m, 1H), 5.05(m, 1H), 5.35(s, 1H), 5.45(d, 1H), 6.85(d, 1H), 7.25(d, 1H), 7.35-7.85(6H), 8.85(dd, 2H), 9.05(m, 1H), 9.35(dd, 2H).

(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-[2*RS*-(4-chlorobenzyl)oxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696c) was synthesized from **600b** via methods used to prepare **690a** from **600b** to afford **696c**. ^{1}H NMR (CD_3OD) δ 1.25(t, 1H), 1.65(q, 1H), 1.9(m, 1H), 2.9(m, 1H),

3.05(m, 1H), 3.9(d, 1H), 4.2(m, 1H), 4.3(d, 1H), 4.7-5.0(m, 3H), 5.25(m, 1H), 5.7(s, 1H), 5.9(d, 1H), 7.5(d, 2H), 7.7-7.9(m, 3H), 8.0(t, 1H), 8.2(m, 2H), 8.75(d, 1H), 9.35(d, 1H).

(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-(2*RS*-cyclopentyloxy-5-oxo-tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696d) was synthesized from **600b** via methods used to prepare **690a** from **600b** to afford **696d**. ^{1}H NMR ($CDCl_3$) δ 0.9(t, 1H), 1.2(t, 1H), 1.3-1.45(m, 2H), 1.6-1.8(m, 4H), 2.45(m, 1H), 2.8(m, 1H), 3.0(m, 1H), 3.4(q, 1H), 3.5(d, 1H), 4.0(m, 2H), 4.2-4.3(m, 2H), 4.55(d, 1H), 4.65(m, 1H), 4.9(m, 1H), 5.05(m, 1H), 5.4(s, 1H), 5.5(d, 1H), 6.8(d, 1H), 7.3-7.9(m, 6H), 8.5(d, 1H), 9.05(d, 1H), 9.4(d, 1H).

(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2*R*,3*S*)-phenethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (696e) was synthesized from **600b** via methods used to prepare **690a** from **600b** to afford **696e**. ^{1}H NMR ($CDCl_3$) δ 1.2(t, 1H), 2.4(m, 1H), 2.8(m, 2H), 3.6(d, 1H), 3.7(q, 1H), 4.0(m, 2H), 4.3(d, 2H), 4.65(m, 1H), 4.85(t, 1H), 5.0(m, 1H), 5.35(d, 1H), 6.5(d, 1H), 7.15-7.85(m, 8H), 8.45(d, 1H), 9.05(d, 1H), 9.4(d, 1H).

Example 32

Table 27

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
688c	200				
689b-1	3.5		2700		
696-1	0.5				
696-2	0.5				
697	1.8		5000		
698	18		13500		
699	1.1				
699a-2					
720	2.7				
721	1.3		5000		
722	5		5000		
723	2.3		2000		
724	2		1800		
725	3.7		3000		
726	300				
727	50		2300		
728	300				
729	28		2800		
730	90		8000		
731	150				
732	5		1800		
733	5		1500		
734	9		6000		
735	6		10000		

Example 33

Compounds **684a**, **688b-1**, **688c**, **689b-1**, **690a-1**, **696-1**, **696-2**, **696a-2**, **696a-1**, **697**, **697a**, **698**, **698a**, **699**, **699a**, **699a-1**, **699a-2**, **800** and **801** were prepared as described below.

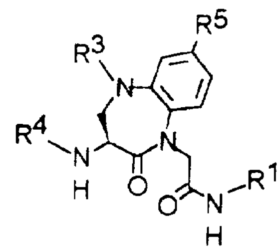


Table 28

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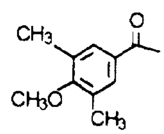
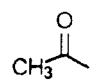
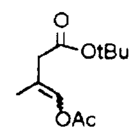
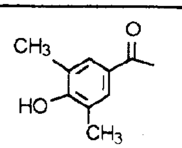
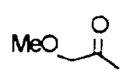
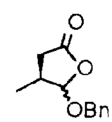
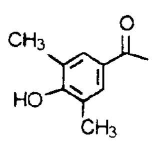
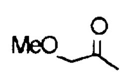
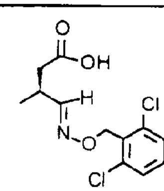
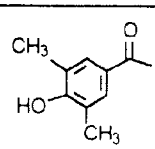
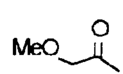
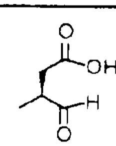
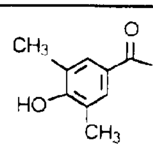
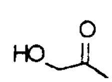
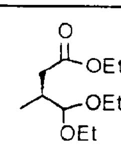
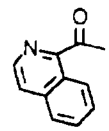
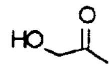
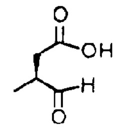
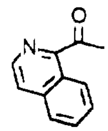
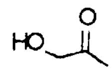
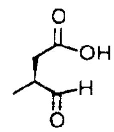
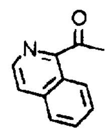
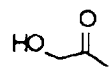
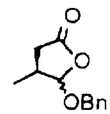
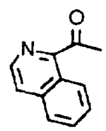
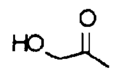
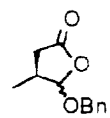
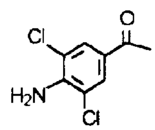
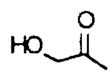
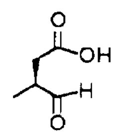
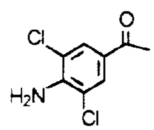
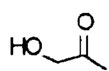
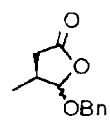
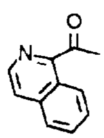
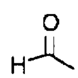
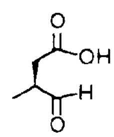
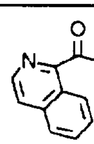
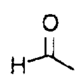
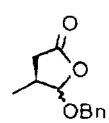
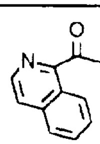
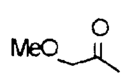
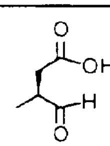
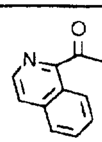
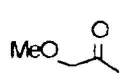
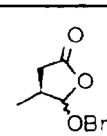
684a			H	
688b-1			F	
688c			H	
689b-1			F	
690a-1			H	

CIP#	R^4	R^3	R^5	R^1
696-1			F	
696-2			Cl	
696a-2			Cl	
696a-1			F	
697			H	
697a			H	
698			H	
698a			H	
699			H	
699a			H	

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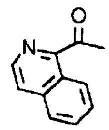
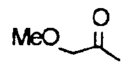
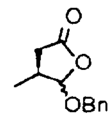
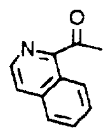
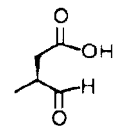
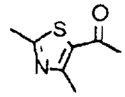
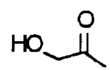
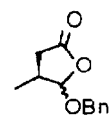
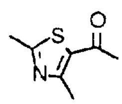
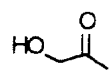
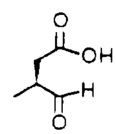
699a-1			F	
699a-2			F	
800			H	
801			H	

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4,4-diethoxybutyric acid ethyl ester(690a-1), was synthesized by the methods used to prepare **690a** and **2100b** to afford **690a-1**, ^{1}H NMR($CDCl_3$) δ 1.15(t, 6H), 1.3(t, 3H), 2.25(s, 6H), 2.60(d, 2H), 3.50(m, 2H), 3.70(m,4H), 4.05(m, 2H), 4.15(m, 2H), 4.30(d, 1H), 4.45(m, 1H), 4.50(d, 1H), 4.55(d, 1H), 4.70(t, 1H), 5.05(m, 1H), 5.30(s, 1H), 6.70(d, 1H), 7.10(d, 2H), 7.30-7.50(m, 7H)

(3*S*)-2-Oxo-3-(3,5-dichloro-4-aminobenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide(697a) was synthesized via methods used to prepare **677** to afford 840 mg of **697a**, ^{1}H NMR ($CDCl_3$) δ 1.78 (br. s, 2H), 2.48-2.58 (d, 0.5H),

2.6-2.7 (m, 0.5H), 2.8-2.9 (m, 0.5H), 2.92-3.03 (m, 0.5H), 3.55-3.8 (m, 2H), 3.92-4.02 (d, 1H), 4.25-4.3 (d, 0.5H), 4.37-4.42 (d, 0.5H), 4.43-4.48 (m,0.5H), 4.55-4.65 (m, 1.5H) 4.7-5.12 (m, 5H), 5.44 (s, 0.5H), 5.58-5.63 (d, 0.5H), 6.95-8.1 (m, 13H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro4-aminobenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid (697) was synthesized via methods used to prepare **2002** from **2001** to afford 140 mg of **697**, ^{1}H NMR (CD_3OD) δ 238-2.5 (m,1H), 2.55-2.75 (m, 1H), 3.68-3.9 (m, 3H), 3.95-4.03 (m, 1H), 4.2-4.3 (m, 1H), 4.4-4.7 (m, 4H), 7.35-7.8 (m, 6H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-acetoxy-3-butenoic acid ethyl ester(684a), was synthesized by the methods used to prepare **2100j** to afford **684a**, ^{1}H NMR (500 MHz, $CDCl_3$ mixture of diastereomers) δ 1.3 (s, 9H), 1.8(s, 3H), 2.1(s, 3H), 2.15(s, 3H), 2.3(s, 6H), 3.3-3.5(m, 3H), 3.65(s, 3H), 3.9(m, 1H), 4.1(d, 1H), 4.3(d, 1H), 4.6-4.8(m, 3H), 5.0(m, 1H), 6.7(s, 1H), 7.0(d, 1H), 7.1(d, 1H), 7.2-7.5(m, 6H).

(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-formyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide(698a) was synthesized via methods used to prepare **652** to afford 795 mg of **698a** ^{1}H NMR (500 MHz, $CDCl_3$ mixture of diastereomers) δ 2.8(m, 2H), 4.0(m, 1H), 4.5-4.8(m, 4H), 5.2(m, 1H), 5.5(s, 1H), 5.75(d,

1H), 7.3-7.85(m, 11H), 7.9(t, 1H), 8.2(d, 1H), 8.6(m, 1H), 9.3(m, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(698) was synthesized via methods used to prepare **653** to afford 225 mg of **698** ^{1}H NMR (500 MHz, CD_3OD) δ 2.4(m, 1H), 2.6(m, 1H), 3.9(m, 1H), 4.2(m, 1H), 4.3-4.7(m, 4H), 5.1(m, 1H), 7.3-7.5(m, 4H), 7.6-7.8(m, 2H), 7.8(m, 2H), 8.2(d, 1H), 8.5(d, 1H), 9.0(d, 1H).

(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide(699a) was synthesized via methods used to prepare **655** to afford 820 mg of **699a** as a tan solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (ddd, 1H), 2.90 (ddd, 1H), 3.20 (s, 3H), 3.25 (s, 3H), 3.70 (t, 1H), 3.90 (m, 2H), 4.20 (dd, 1H), 4.60 (m, 2H), 4.70-5.00 (m, 5H), 5.55 (d, 1H), 7.00 (d, 1H), 7.20-7.50 (m, 7H), 8.45 (dd, 1H), 9.0 (dd, 1H), and 9.35 ppm (dd, 1H).

(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(688b-1) was synthesized via methods used to prepare **655** to afford 600 mg of **688b-1**, ^{1}H NMR ($CDCl_3$; mix. of diastereomers) δ 2.21 (s, 3H), 2.28 (s, 3H), 2.42-2.50 (m, 0.5 H), 2.58-2.65 (m, 0.5H), 2.83-2.91 (m, 0.5H), 2.98-3.1 (m, 0.5H), 3.18 (s,1.5H), 3.22 (s, 1.5H), 3.72-3.78 (d, 1H), 3.78-3.9 (m, 2H), 4.08-4.15 (d, 1H), 4.5-4.69 (m, 3H), 4.7-

4.85 (m, 1H), 4.88-5.1 (m, 2H), 5.45 (s, 0.5H), 5.55-5.65 (d, 0.5H), 6.85-6.92 (m, 1H), 7.02-7.13 (m, 2H), 7.24-7.55(m, 9H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(689b-1) was synthesized via methods used to prepare **2002** from **2001** to afford **689b-1**, ^{1}H NMR (CD_3OD) δ 2.18 (s, 6H), 2.36-2.47 (m, 1H), 2.6-2.72 (m, 1H), 3.34 (s, 3H), 3.66-3.88 (m, 2H), 3.95-4.05 (m, 1H), 4.2-4.78 (m, 5H), 4.9 (m, 1H), 7.3-7.41 (m, 2H), 7.48 (s, 2H), 7.5-7.63 (m, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(699) was synthesized via methods used to prepare **2002** from **2001** to afford **699** as a white solid, ^{1}H NMR (500 MHz, CD_3OD) δ 2.50 (m, 1H), 2.70 (m, 1H), 3.25 (s, 3H), 3.80 (bd, 1H), 3.90 (bd, 1H), 4.00 (bd, 1H), 4.30 (m, 1H), 4.50-4.70 (m, 3H), 4.80-4.85 (bt, 1H), 5.00 (bm, 1H), 7.40-7.55 (m, 5H), 7.70 (bm, 1H), 7.85 (bm, 1H), 8.00 (bm, 1H), 8.55 (bd, 1H), and 9.05 ppm (bd, 1H).

(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(696a-1) was synthesized via methods used to prepare **656** to afford **800** as a yellow solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 (ddd, 1H), 2.85 (ddd, 1H), 3.70-3.80 (m, 2H), 3.95 (bm, 1H), 4.05 (d, 1H), 4.30 (d, 1H), 4.40-4.60 (m, 4H), 4.70- 5.05 (m, 4H), 5.55

(d, 1H), 7.10 (d, 1H), 7.20-7.35 (m, 3H), 7.40- 7.50 (m, 1H), 7.60- 7.85 (m, 3H), 8.40 (dd, 1H), 9.10 (m, 1H), and 9.30 pp (m, 1H).

(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-chloro-1*H*-1,5-benzodiazepine-1-acetamide(696a-2) was synthesized via methods used to prepare **677**, to afford 204 mg of **696a-2** as a white solid,with the exception that the reduction of the nitro- group was done as follows: To a solution of the nitro compound (7.2 g, 20 mmol) in MeOH was added NH_4Cl (2.1 g, 39 mmol) and Zn (17 g, 260 mmol). The resulting mixture was heated to reflux 1 hour after which it was cooled and filtered through celite. The filtrated was concentrated *in vacuo* then treated with cold 1N HCl to afford 3.6 g of a pale red solid. ^1H NMR($CDCl_3$) δ 1.85(s, 1H), 2.45(d, 0.5H), 2.50-2.65(m, 0.5H), 2.80-2.90(m, 0.5H), 2.90-3.00(m, 0.5H), 3.45(s, 0.5H), 3.55-3.75(m, 1H), 3.85-4.15(m, 2H), 4.25(d, 1H), 4.40-4.65(m, 2H), 4.70-4.80(m, 0.5H), 4.85-5.15(m, 3H), 5.40(s, 0.5H), 5.60(d, 0.5H), 7.00(d, 0.5H), 7.15-7.90(m, 12.5H), 8.35-8.45(m, 1H), 9.00-9.10(m, 1H), 9.25-9.40(m, 1H)

(3*S*)-3-[(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(696-1) was synthesized via methods used to prepare **2002** from **2001** to afford 140 mg of **696-1** as a white solid, ^1H NMR (500 MHz, CD_3OD) δ 2.50 (m, 1H), 2.70 (m, 1H), 3.85 (d, 1H), 3.95 (m, 1H), 4.10 (d, 1H), 4.35 (m, 1H), 4.50-4.60 (m, 2H), 4.80 (bm, 1H), 5.00 (m, 1H), 7.40- 7.48

(m, 3H), 7.65 (m, 1H), 7.75 (t, 1H), 7.85 (t, 1H), 8.00 (d, 1H), 8.55 (d, 1H), and 9.05 ppm (d, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-2,3,4,5-tetrahydro-7-chloro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(696-2) was synthesized via methods used to prepare **2002** from **2001** to afford 250 mg of **696-2**as a white solid, ^{1}H NMR(CD_3OD) δ 2.40-2.55(m, 1H), 2.60-2.75(m, 1H), 3.80-4.00(m, 2H), 4.05(d, 1H), 4.20-4.35(m, 1H), 4.45-4.65(m, 3H), 4.80-5.10(m, 2H)

(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(699a-1) was synthesized via methods used to prepare **655** to afford **699a-1** ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 (ddd, 1H), 2.90 (ddd, 1H), 3.25 (s, 3H), 3.28 (s, 3H), 3.80 (bt, 2H), 3.95 (bm, 2H), 4.25 (dd, 1H), 4.45-4.90 (m, 3H), 5.60 (d, 1H), 7.05- 7.40 (m, 8H), 7.50 (bm, 1H), 7.65- 7.85 (m, 2H), 8.45 (d, 1H), 9.1 (m, 1H), and 9.35 ppm (m, 1H)

(3*S*)-3-[(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(699a-2) was synthesized via methods used to prepare **2002** from **2001** to afford **699a-2** ^{1}H NMR (500 MHz, CD_3OD) δ 2.51 (m, 1H), 2.70 (dt, 1H), 3.31 (bs, 3H), 3.90 (bdt, 1H), 3.95 (bm, 1H), 4.05 (d, 1H), 4.35 (m, 1H), 4.50 (d, 1H), 4.60 (dd, 1H), 4.65 (dt, 1H), 4.80 (m, 1H), 5.05 (m, 1H), 7.35- 7.48 (m, 3H), 7.65 (bm, 1H), 7.75 (t,

1H), 7.82 (t, 1H), 8.05 (d, 1H), 8.55 (d, 1H), and 9.05 ppm (d, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid, O-2,6-dichlorobenzyl oxime(688c) was synthesized via methods used to prepare **308d** to afford **800**, ^{1}H NMR (CD_3OD) δ 2.2 (s, 6H), 2.58-2.83 (m, 2H), 3.28 (s, 3H), 3.29-3.34 (m, 1H), 3.68-3.80 (m, 2H), 3.95-4.05 (dd, 1H), 4.38-4.48 (dd, 1H), 4.82-5.00 (m, 2H), 5.26-5.36 (m, 2H), 7.22-7.65 (m, 10H).

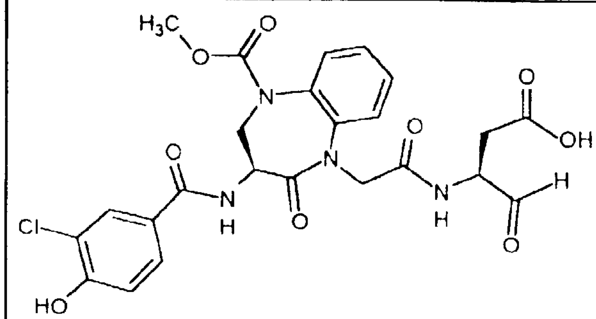
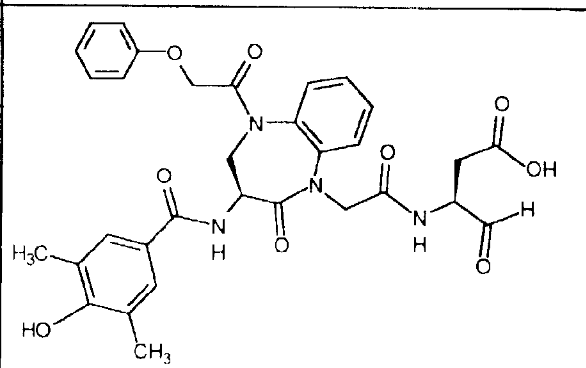
(3*S*)-2-Oxo-(2,4-dimethylthiazo-5-yl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide(800) was synthesized via methods used to prepare **696a-1** to afford 204 mg of **800** as a yellow solid, ^{1}H NMR($CDCl_3$)(mixture of diastereomers) δ 1.70(s, 1H), 2.40-2.80(m, 7H), 2.80-2.90(m, 0.5H), 2.95-3.05(m, 0.5H), 3.30-3.35(m, 0.5H), 3.45-3.55(m, 0.5H), 3.55-3.65(m, 1H), 3.80-4.05(m, 2H), 4.30-4.50(m, 2H), 4.55-4.65(m, 1H), 4.75-4.95(m, 3H), 5.45(s, 0.5H), 5.55(d, 0.5H), 6.70(d, 0.5H), 6.90(d, 0.5H), 7.15-7.80(m, 10H)

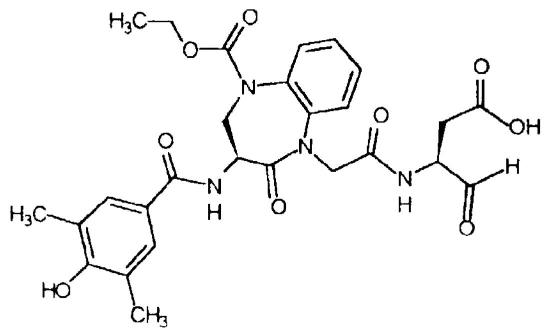
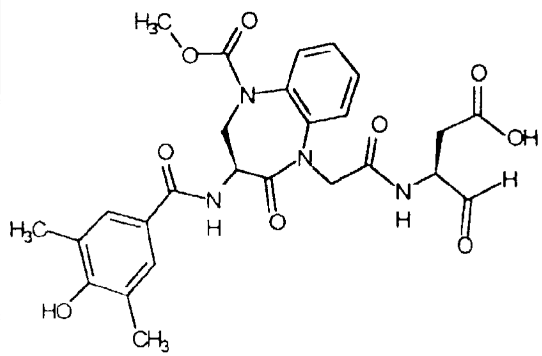
(3*S*)-3-[(3*S*)-2-Oxo-3-(2,4-dimethylthiazo-1-oyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(801) was synthesized via methods used to prepare **2002** from **2001** to afford **801**.

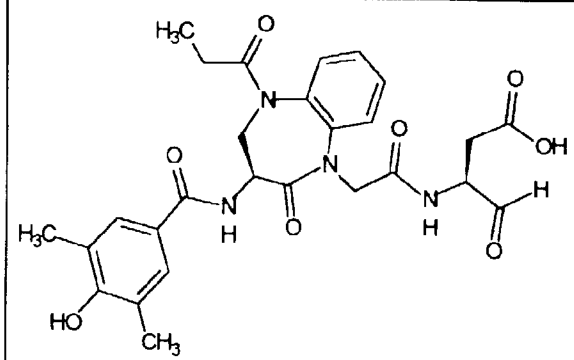
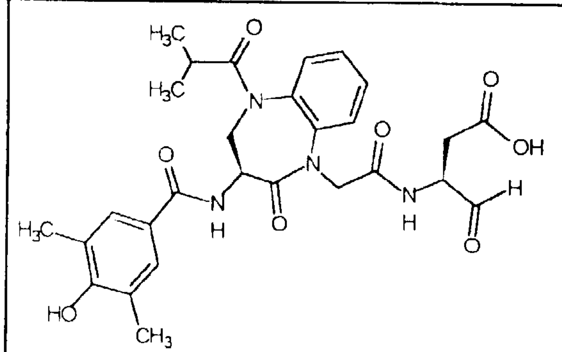
Example 34

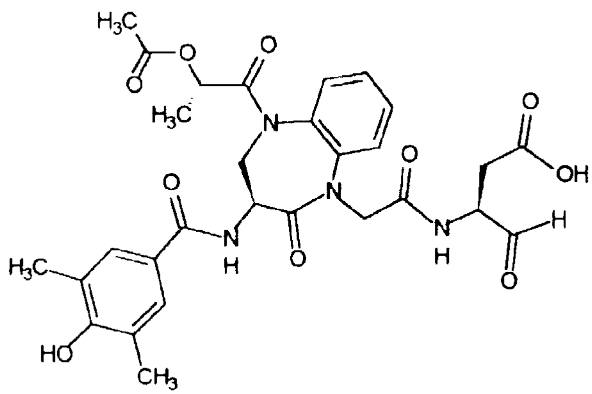
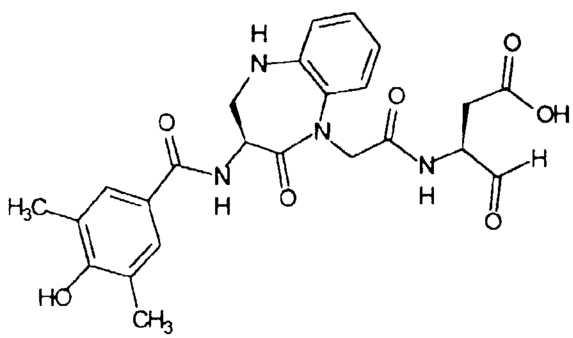
Compounds **720-73** were prepared by methods similar to the methods used to prepare compounds 619-635 (see, Example 13). Physical data for compounds **720-73** is listed in Table 29.

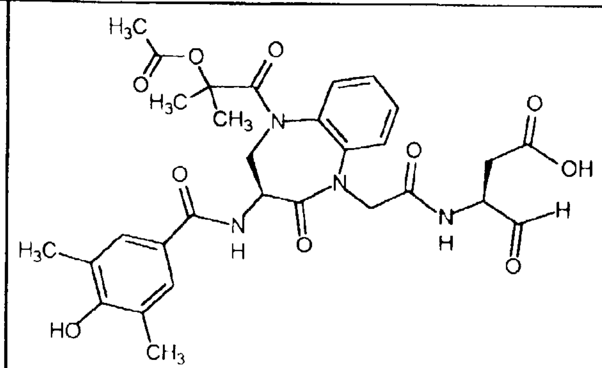
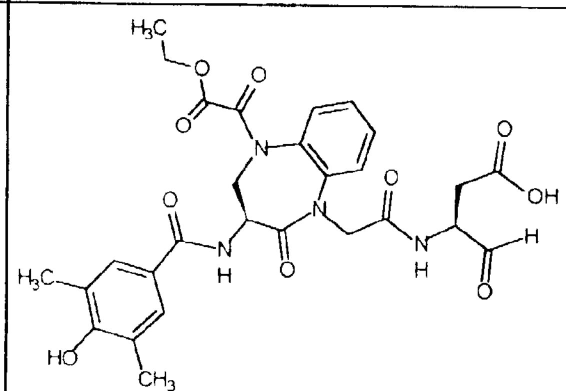
Table 29

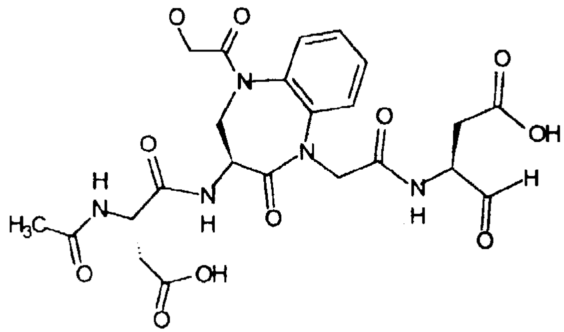
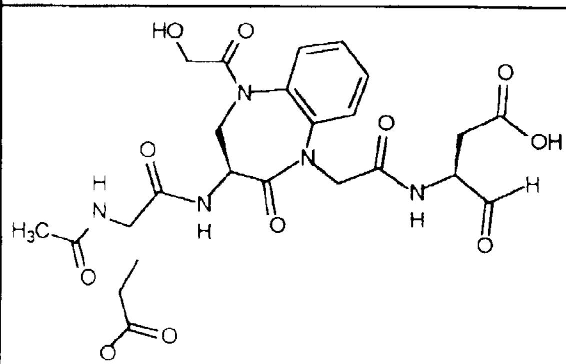
Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
720		C24H23ClN4O9	546.93	10.729 99%	568.8
721		C32H32N4O9	616.63	13.241 99%	640.4

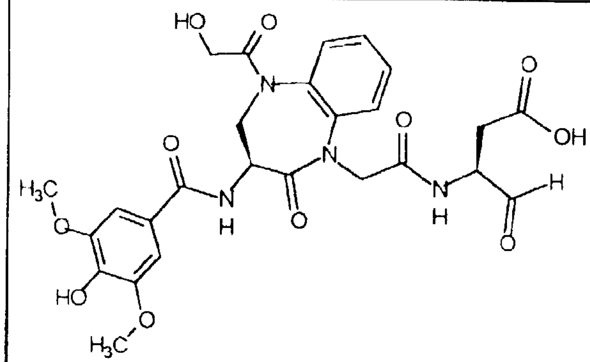
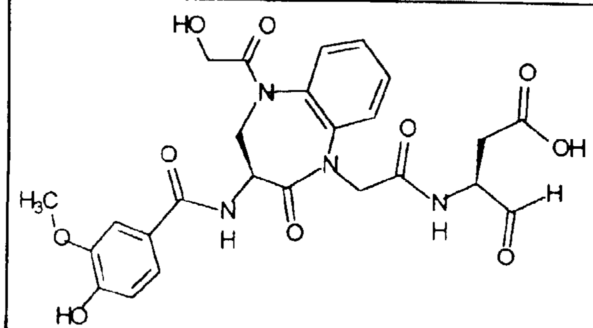
Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
722		C27H30N4O9	554.56	11.761 99%	578.2
723		C26H28N4O9	540.53	10.655 79%	564.5

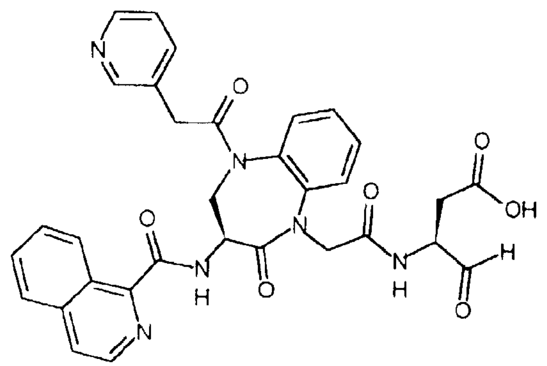
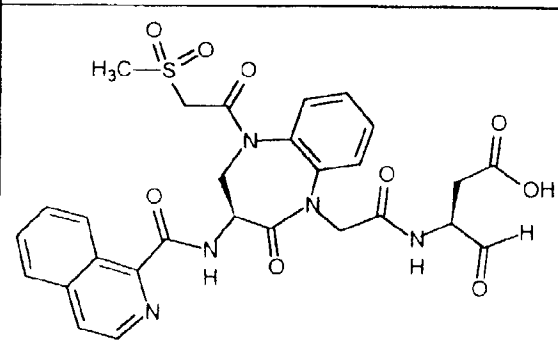
Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
724		C27H30N4O8	538.56	10.584 99%	563.1
725		C28H32N4O8	552.59	11.329 99%	577.2

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
726		C29H32N4O10	596.60	10.667 99%	620.8
727		C24H26N4O7	482.50	9.085 92%	506.6

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
728		C30H34N4O10	610.63	11.556	634.9
729		C28H30N4O10	582.57	11.611 99%	607.3

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
730		C23H27N5O11	549.50	3.939 96%	572.2
731		C24H29N5O11	563.53	4.298 92%	587

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
732		C26H28N4O11	572.53	7.640 98%	595.9
733		C25H26N4O10	542.51	7.375 98%	565.9

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
734		C32H28N6O7	608.62	9.656 99%	630.6
735		C28H27N5O9S	609.62	10.887 92%	632.1

Example 35

Compounds **736-767** were prepared by methods similar to the methods used to prepare compounds **619-635** (see, Example 13). Physical data for compounds **736-767** is listed in Table 30.

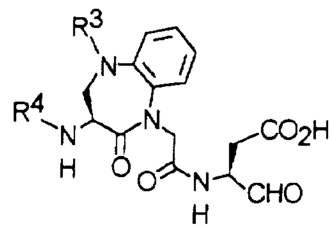
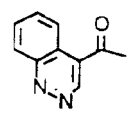
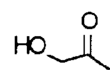
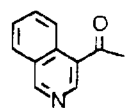
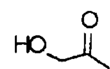
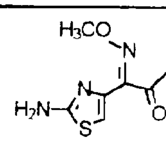
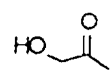
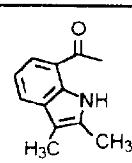
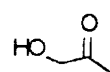
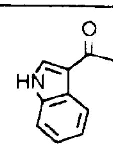
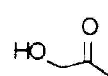
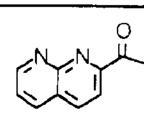
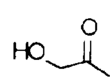
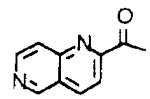
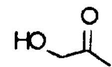
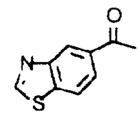
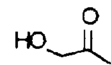
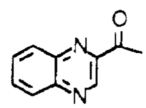
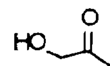
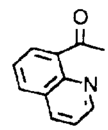
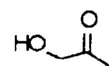
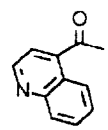
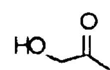
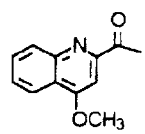
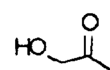
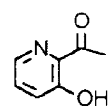
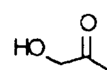
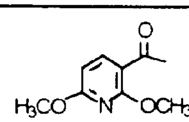
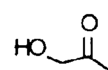
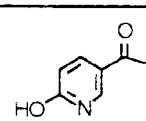
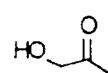
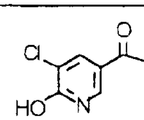
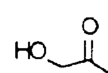
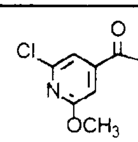
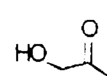
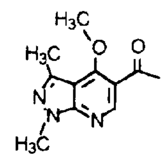
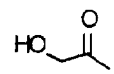
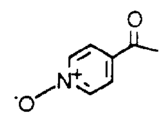
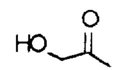
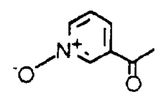
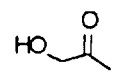
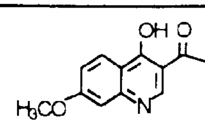
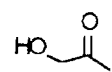
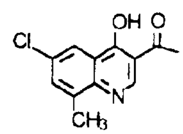
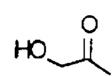
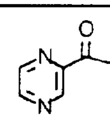
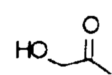
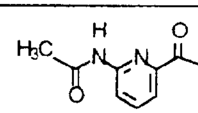
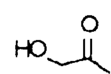
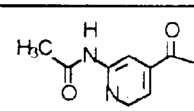
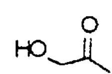
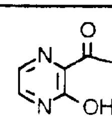
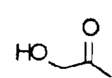
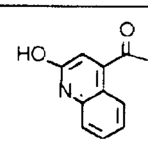
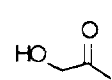
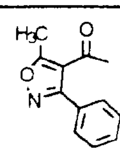
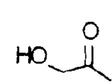
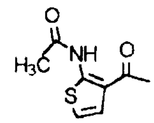
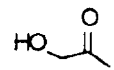
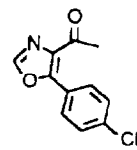
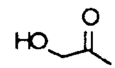
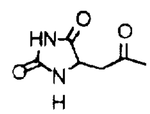
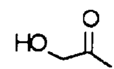
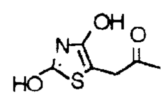
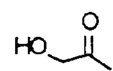


Table 30

Compound	R^4	R^3
736		
737		
738		
739		
740		
741		

Compound	R^4	R^3
742		
743		
744		
745		
746		
747		
748		
749		
750		
751		
752		

Compound	R^4	R^3
753		
754		
755		
756		
757		
758		
759		
760		
761		
762		
763		

Compound	R^4	R^3
764		
765		
766		
767		

The data of the examples above demonstrate that compounds according to this invention display inhibitory activity towards IL-1ß Converting Enzyme.

Insofar as the compounds of this invention are able to inhibit ICE in vitro and furthermore, may be delivered orally to mammals, they are of evident clinical utility for the treatment of IL-1-, apoptosis-, IGIF-, and IFN-γ mediated diseases. These tests are predictive of the compounds ability to inhibit ICE _in vivo_.

While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and processes of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.

CLAIMS

We claim:

1. A compound represented by the formula:

α

$$
\begin{array}{l}
\qquad\qquad\quad (CJ_2)_m\text{-}T \\
\qquad\qquad\quad / \\
R_1\text{-}NH\text{-}X_1 \\
\qquad\qquad\quad \backslash \\
\qquad\qquad\quad (CH_2)_g\text{-}R_3
\end{array}
$$

wherein:

X_1 is -CH;

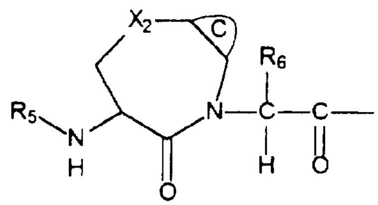
g is 0 or 1;

each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

m is 0, 1, or 2;

T is -OH, $-CO-CO_2H$, $-CO_2H$, or any bioisosteric replacement for $-CO_2H$;

R_1 is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q_1, at any nitrogen by R_5, or at any atom by =O, -OH, $-CO_2H$, or halogen; and any saturated ring may optionally be unsaturated at one or two bonds;

(w)  ;

wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is:

$-CN$,

$-CH{=}CH-R_9$,

$-CH{=}N-O-R_9$,

$-(CH_2)_{1-3}-T_1-R_9$,

$-CJ_2-R_9$,

$-CO-R_{13}$, or

$-CO-CO-N\begin{matrix}/R_5\\ \backslash R_{10}\end{matrix}$;

each R_4 is independently selected from the group consisting of:

$-H$,

$-Ar_1$,

$-R_9$,

$-T_1-R_9$, and

$-(CH_2)_{1,2,3}-T_1-R_9$;

each T_1 is independently selected from the group consisting of:

$CH{=}CH-$,

$-O-$,

$-S-$,
$-SO-$,
$-SO_2-$,
$-NR_{10}-$,
$-NR_{10}-CO-$,
$-CO-$,
$-O-CO-$,
$-CO-O-$,
$-CO-NR_{10}-$,
$-O-CO-NR_{10}-$,
$-NR_{10}-CO-O-$,
$-NR_{10}-CO-NR_{10}-$,
$-SO_2-NR_{10}-$,
$-NR_{10}-SO_2-$, and
$-NR_{10}-SO_2-NR_{10}-$;

each R_5 is independently selected from the group consisting of:

$-H$,
$-Ar_1$,
$-CO-Ar_1$,
$-SO_2-Ar_1$,
$-CO-NH_2$,
$-SO_2-NH_2$,
$-R_9$,
$-CO-R_9$,
$-CO-O-R_9$,
$-SO_2-R_9$,

$$-CO-N\begin{matrix}/Ar_1\\ \backslash R_{10}\end{matrix},$$

$$-SO_2-N\begin{matrix}/Ar_1\\ \backslash R_{10}\end{matrix},$$

$$-CO-N\begin{matrix} /R_9 \\ \backslash R_{10}, \end{matrix}$$ and

$$-SO_2-N\begin{matrix} /R_9 \\ \backslash R_{10}; \end{matrix}$$

R_6 is:
-H
$-Ar_1$,
$-R_9$,
$-(CH_2)_{1,2,3}-T_1-R_9$, or
an α-amino acid side chain residue;

each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted with -OH, -F, or =O and optionally substituted with one or two Ar_1 groups;

each R_{10} is independently selected from the group consisting of -H or a C_{1-6} straight or branched alkyl group;

each R_{13} is independently selected from the group consisting of $-Ar_2$, $-R_4$ and $-N(R_5)-OH$;

each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring

atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, $-SO_2-$, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted with $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN,

```
                                    O
                                   / \
=O, -OH, -perfluoro C1-3 alkyl,       CH2,   or -Q1;
                                   \ /
                                    O
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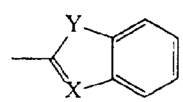
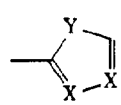
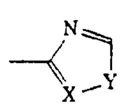
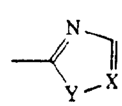
each Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ and $-Q_2$:

(hh)  ;

(ii)  ;

(jj)  ; and

(kk)  ;

each Q_1 is independently selected from the group consisting of:

$-Ar_1$

$-O-Ar_1$

$-R_9$,

$-T_1-R_9$, and

$-(CH_2)_{1,2,3}-T_1-R_9$;

each Q_2 is independently selected from the group consisting of -OH, $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, $-CF_3$, and

```
 O
/ \
   CH2;
\ /
 O
```

provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1;

each X is independently selected from the group consisting of =N-, and =CH-;

each X_2 is independently selected from the group consisting of -O-, $-CH_2-$, -NH-, -S-, -SO-, and $-SO_2-$;

each Y is independently selected from the group consisting of -O-, -S-, and -NH;

provided that when

g is 0,

J is -H,

m is 1,

T is $-CO_2H$,

X_2 is O,

R_5 is benzyloxycarbonyl, and

ring C is benzo,

then R_3 cannot be $-CO-R_{13}$ when:

R_{13} is $-CH_2-O-Ar_1$ and

Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with a chlorine atom;

or when

R_{13} is $-CH_2-O-CO-Ar_1$, wherein

Ar_1 is 2,6-dichlorophenyl.

2. The compound according to claim 1, wherein:

X_1 is -CH;

g is 0;

J is -H;

m is 0 or 1 and T is $-CO-CO_2H$, or any bioisosteric replacement for $-CO_2H$, or

m is 1 and T is $-CO_2H$;

ring C is benzo optionally substituted with $-C_{1-3}$ alkyl, $-O-C_{1-3}$ alkyl, -Cl, -F or $-CF_3$;

R_5 is:

$-CO-Ar_1$

$-SO_2-Ar_1$,

$-CO-NH_2$,

$-CO-NH-Ar_1$

$-CO-R_9$,

-CO-O-R_9,
-SO_2-R_9, or
-CO-NH-R_9,

R_7 is -H and R_6 is: -H,
-R_9, or
-Ar_1;

R_9 is a C_{1-6} straight or branched alkyl group optionally substituted with =O and optionally substituted with -Ar_1;

R_{10} is H or a -C_{1-3} straight or branched alkyl group;

Ar_1 is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl optionally substituted with -O-C_{1-3} alkyl, -NH-C_{1-3} alkyl, -N-(C_{1-3} alkyl)$_2$, -Cl, -F, -CF_3, -C_{1-3} alkyl, or

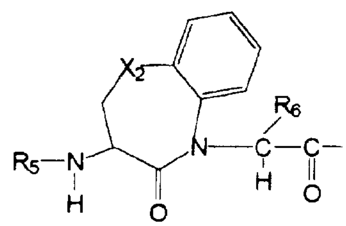
```
 O
/ \
   CH2  ;
\ /
 O
```

Q_1 is R_9 or -$(CH_2)_{0,1,2}$-T_1-$(CH_2)_{0,1,2}$-Ar_1, wherein T_1 is -O- or -S-;

each X is independently selected from the group consisting of =N-, and =CH-;

each X_2 is independently selected from the group consisting of -O-, -CH_2-, -NH-, -S-, -SO-, and -SO_2-.

3. The compound according to claims 1 or 2, wherein the R_1 group is:

(w1)  ; wherein

X_2 is:

-O- ,

-S- ,

$-SO_2-$, or

-NH-;

optionally substituted with R_5 or Q_1 at X_2 when X_2 is -NH-; and

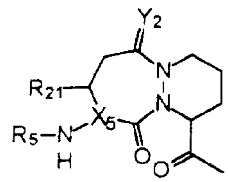
ring C is benzo substituted with $-C_{1-3}$ alkyl, $-O-C_{1-3}$ alkyl, -Cl, -F or $-CF_3$.

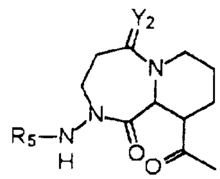
4. A compound represented by the formula:

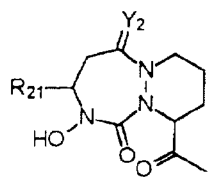
$$(\underline{I}) \qquad R_1-\underset{\displaystyle H}{\underset{|}{N}}-R_2$$

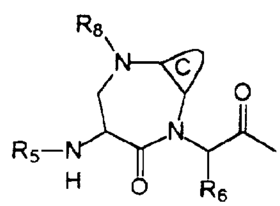
wherein:

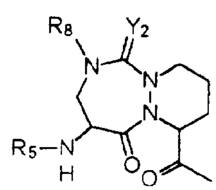
R_1 is selected from the group consisting of the following formulae:

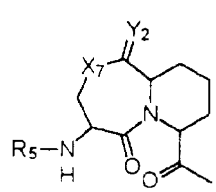
(e10)  ;

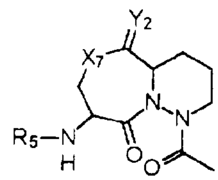
(e11)  ;

(e12)  ;

(w2)  ;

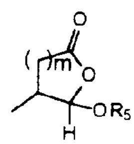
(y1)  ;

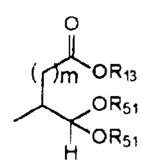
(y2)  ;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_2 is:

(a)  , or

(b)  ;

m is 1 or 2;

R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$$-C(O)-N\begin{matrix}/R_{10}\\ \backslash R_{10}\end{matrix},$$

$-S(O)_2-R_9$,

$-C(O)-CH_2-O-R_9$,

$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$, and
$-C(O)C(O)-OR_{10}$;

X_5 is $-\underset{|}{C}H-$ or $-\underset{|}{N}-$;

Y_2 is H_2 or O;

X_7 is $-N(R_8)-$ or $-O-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(H)-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$;
$-C(O)-CH_2N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
$-H$, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9, $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

```
   O
  / \
     CH2,
  \ /
   O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

5. The compound according to claim 4, wherein R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

6. The compound according to claim 4, wherein R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$.

7. The compound according to claims 5 or 6, wherein:

m is 1;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is $-H$ or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

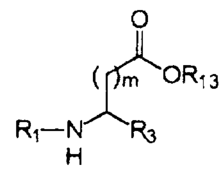
each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
 O
/ \
   CH2,
\ /
 O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

8. A compound represented by the formula:

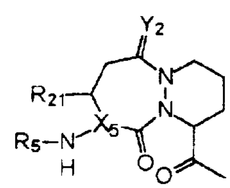
(II) 

wherein:

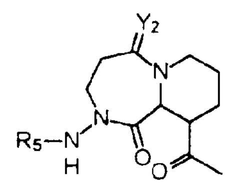
m is 1 or 2;

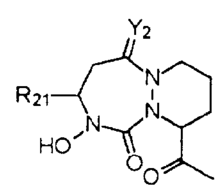
R_1 is selected from the group consisting of the following formulae:

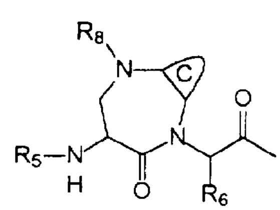
(e10)

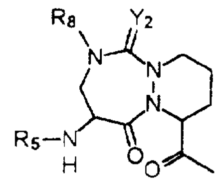


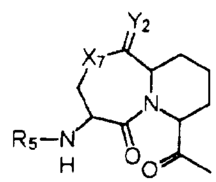
, wherein X_5 is N;

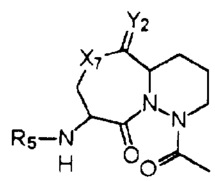
(e11)  ;

(e12)  ;

(w2)  ;

(y1)  ;

(y2)  ;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

-C(O)-CH_2-T_1-R_{11},

-C(O)-CH_2-F,

-C=N-O-R_9, and

-CO-Ar_2;

R_5 is selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9,

$$-C(O)-N\begin{cases} R_{10} \\ R_{10}, \end{cases}$$

$-S(O)_2-R_9$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$, and
$-C(O)C(O)-OR_{10}$,

Y_2 is H_2 or O;

X_7 is $-N(R_8)-$ or $-O-$;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
$-H$, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

$-Ar_4$,

$-(CH_2)_{1-3}-Ar_4$,

-H, and

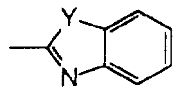
$-C(O)-Ar_4$;

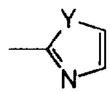
R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

OR_{13} is optionally -N(H)-OH;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

```
   O
  / \
     CH2;
  \ /
   O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

9. The compound according to claim 8, wherein R_1 is (e11).

10. The compound according to claim 8, wherein R_1 is (e12).

11. The compound according to claim 8, wherein R_1 is (y1).

12. The compound according to claim 8, wherein R_1 is (y2).

13. The compound according to claim 8, wherein and R_1 is (z).

14. The compound according to claim 8, wherein R_1 is (w2).

15. The compound according to claim 14, wherein:

m is 1;

ring C is benzo, pyrido, or thieno;

R_3 is selected from the group consisting of -C(O)-H, -C(O)-Ar_2, and -C(O)CH_2-T_1-R_{11};

R_5 is selected from the group consisting of:

-C(O)-R_{10}, wherein R_{10} is -Ar_3;

-C(O)O-R_9, wherein R_9 is -CH_2-Ar_3;

-C(O)C(O)-R_{10}, wherein R_{10} is -Ar_3;

-R_9, wherein R_9 is a C_{1-2} alkyl group substituted with -Ar_3; and

-C(O)C(O)-OR_{10}, wherein R_{10} is -CH_2Ar_3;

T_1 is O or S;

R_6 is H;

R_8 is selected from the group consisting -C(O)-R_{10}, -C(O)-CH_2-OR_{10}, and -C(O)CH_2-N(R_{10})(R_{10}), wherein R_{10} is H, CH_3, or -CH_2CH_3;

R_{11} is selected from the group consisting of -Ar_4, -$(CH_2)_{1-3}$-Ar_4, and -C(O)-Ar_4;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with -Ar_3, -OH, -OR_9, -CO_2H, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

16. The compound according to claim 8, wherein R_1 is (e10) and X_5 is N.

17. The compound according to claim 16, wherein R_3 is $CO-Ar_2$.

18. The compound according to claim 16, wherein R_3 is $-C(O)-CH_2-T_1-R_{11}$ and R_{11} is $-(CH_2)_{1-3}-Ar_4$.

19. The compound according to claim 16, wherein:

R_3 is $-C(O)-CH_2-T_1-R_{11}$;

T_1 is O; and

R_{11} is $-C(O)-Ar_4$.

20. The compound according to claim 16, wherein R_3 is $-C(O)-H$.

21. The compound according to claim 16, wherein R_3 is $-CO-CH_2-T_1-R_{11}$ and R_{11} is $-Ar_4$.

22. The compound according to any one of claims 19-21, wherein R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

23. The compound according to claim 22, wherein:

m is 1;

T_1 is O or S,

provided that when R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
   O
  / \
     CH2,
  \ /
   O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

24. The compound according to any one of claims 19-21, wherein R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-C(O)-R_{10}$,
$-R_9$, and
$-C(O)-C(O)-OR_{10}$.

25. The compound according to claim 24, wherein:

m is 1;

T_1 is O or S,

provided that when R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, $-CO_2H$,

wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

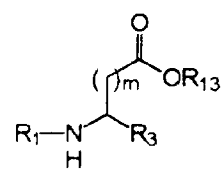
each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

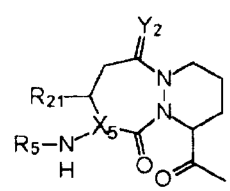
26. A compound represented by the formula:

(<u>II</u>) 

wherein:

m is 1 or 2;

R_1 is:

(e10)  ;

R_3 is $-CO-Ar_2$;

R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$$-C(O)-N\begin{matrix} / R_{10} \\ \backslash R_{10} \end{matrix},$$

$-S(O)_2-R_9$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$, and
$-C(O)C(O)-OR_{10}$,

X_5 is CH;

Y_2 is H_2 or O;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

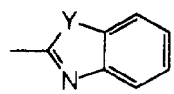
R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

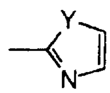
OR_{13} is optionally -N(H)-OH;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following

group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally

containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

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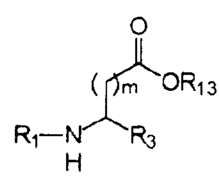
   O
  / \
     CH2;
  \ /
   O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

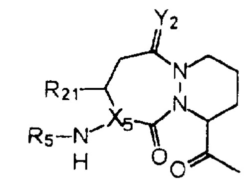
27. A compound represented by the formula:

(II) 

wherein:

m is 1 or 2;

R_1 is:

(e10)  ;

R_3 is $-C(O)-CH_2-T_1-R_{11}$ and R_{11} is $-(CH_2)_{1-3}-Ar_4$;

R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$$-C(O)-N\begin{array}{l} \diagup R_{10} \\ \diagdown R_{10}, \end{array}$$

$-S(O)_2-R_9$,

$-C(O)-CH_2-O-R_9$,

$-C(O)C(O)-R_{10}$,

$-R_9$,

$-H$, and

$-C(O)C(O)-OR_{10}$,

X_5 is CH;

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group

consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

OR_{13} is optionally -N(H)-OH;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said

heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, $-R_5$, $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

```
   O
  / \
     CH2;
  \ /
   O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

28. The compound according to claims 26 or 27, wherein R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

29. The compound according to claim 28, wherein:

m is 1;

T_1 is O or S;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

30. The compound according to claims 26 or 27, wherein R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-C(O)-R_{10}$,
$-R_9$, and
$-C(O)-C(O)-OR_{10}$.

31. The compound according to claim 30, wherein:

m is 1;

T_1 is O or S;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl,

wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

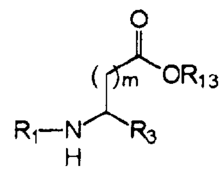
```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted

with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

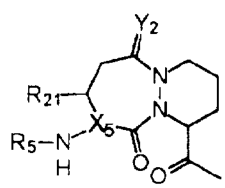
32. A compound represented by the formula:

(II) 

wherein:

m is 1 or 2;

R_1 is:

(e10)  ;

R_3 is $-C(O)-CH_2-T_1-R_{11}$; T_1 is O; and R_{11} is $-C(O)-Ar_4$;

R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$;

X_5 is CH;

Y_2 is H_2 or O;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

OR_{13} is optionally -N(H)-OH;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,

and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

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 O
/ \
   CH2;
\ /
 O
```
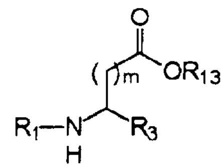

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

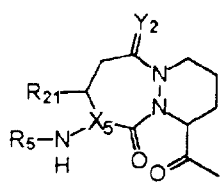
33. A compound represented by the formula:

(II) 

wherein:

m is 1 or 2;

R_1 is:

(e10)  ;

R_3 is -C(O)-H;

R_5 is selected from the group consisting of:

-S(O)$_2$-R_9,

-S(O)$_2$-NH-R_{10},

-C(O)-C(O)-R_{10},

-R_9, and

-C(O)-C(O)-OR_{10};

X_5 is CH;

Y_2 is H_2 or O;

each R_9 is independently selected from the group consisting of -Ar_3 and a -C_{1-6} straight or branched alkyl group optionally substituted with -Ar_3, wherein the -C_{1-6} alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, -Ar_3, a -C_{3-6} cycloalkyl group, and a

$-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

OR_{13} is optionally -N(H)-OH;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

```
   O
  / \
     CH2;
  \ /
   O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

34. The compound according to claims 32 or 33, wherein:

m is 1;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl,

pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

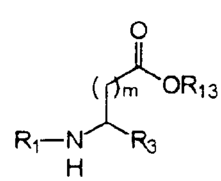
each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

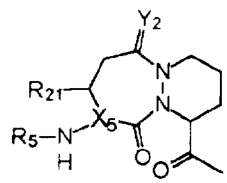
35. A compound represented by the formula:

(II) 

wherein:

m is 1;

R_1 is:

(e10)  ;

R_3 is $-CO-CH_2-T_1-R_{11}$ and R_{11} is $-Ar_4$;

R_5 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$, and
$-C(O)-NH-R_{10}$;

X_5 is CH;

Y_2 is O;

T_1 is O or S;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl,

wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

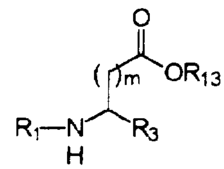
```
    O
   / \
      CH2,
   \ /
    O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$

groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

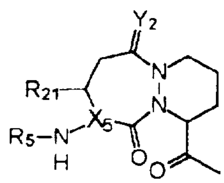
36. A compound represented by the formula:

(II) 

wherein:

m is 1;

R_1 is:

(e10) 
;

R_3 is $-CO-CH_2-T_1-R_{11}$ and R_{11} is $-Ar_4$;

R_5 is selected from the group consisting of:
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-C(O)-R_{10}$,
$-R_9$, and
$-C(O)-C(O)-OR_{10}$;

X_5 is CH;

Y_2 is O;

T_1 is O or S;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
      O
     / \
        CH2,
     \ /
      O
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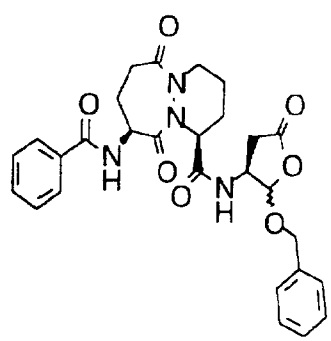
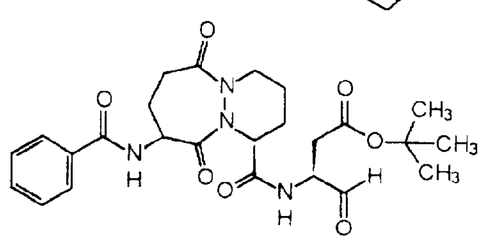
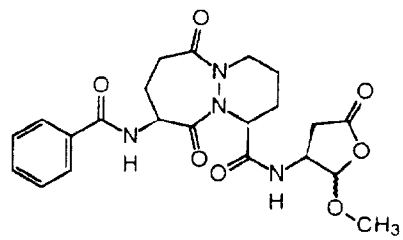
wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

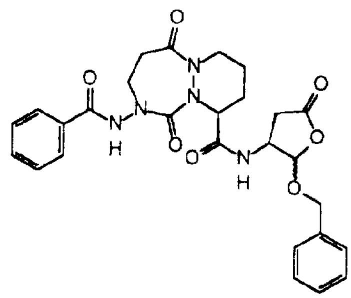
provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

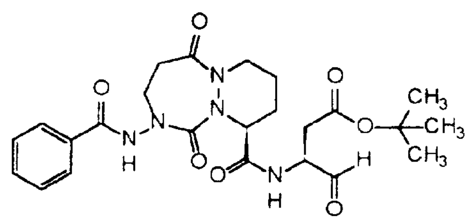
37. The compound according to claim 7 selected from the group consisting of:

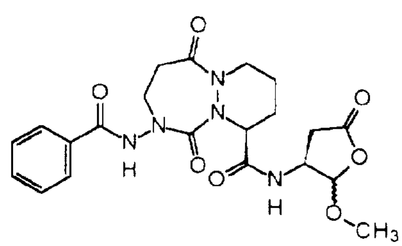
213e  ;

302  ;

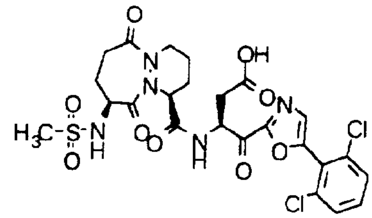
304a  ;

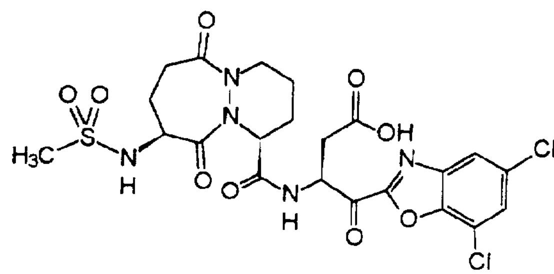
813e  ;

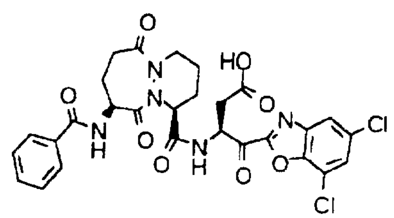
902  ; and

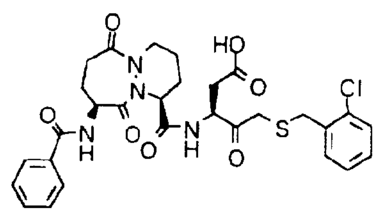
904a  .

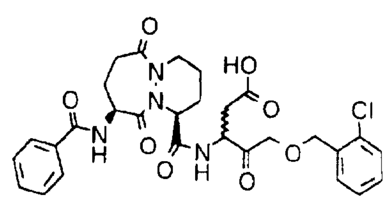
38. The compound according to claims 8 or 68, selected from the group consisting of:

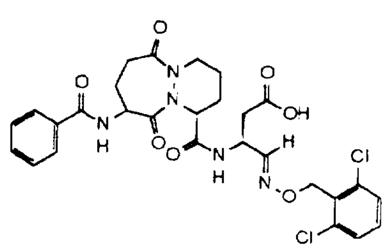
220b  ;

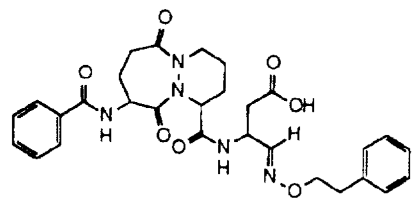
223b  ;

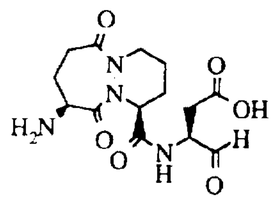
223e  ;

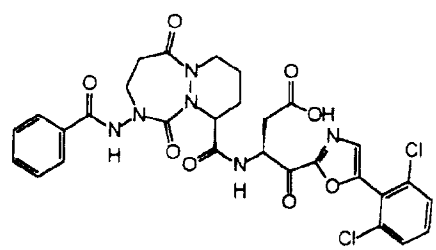
226e  ;

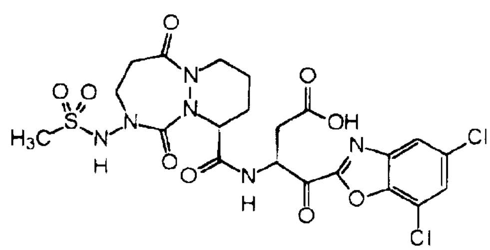
227e  ;

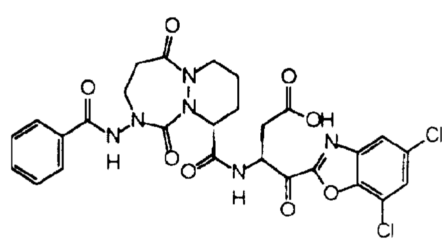
307a  ;

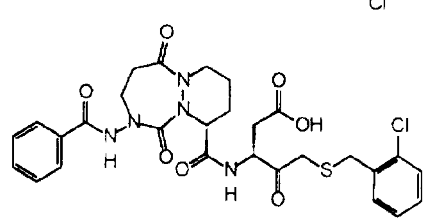
307b  ;

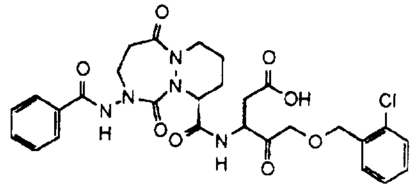
429  ;

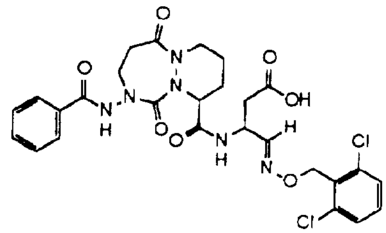
820b  ;

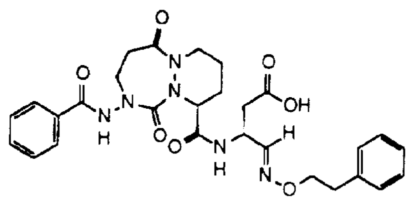
823b  ;

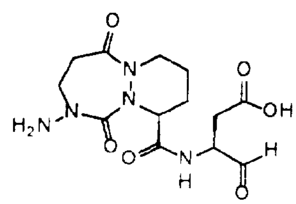
823e  ;

826e  ;

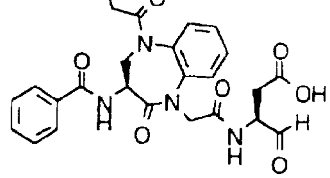
827e  ;

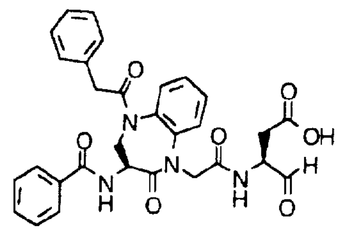
907a  ;

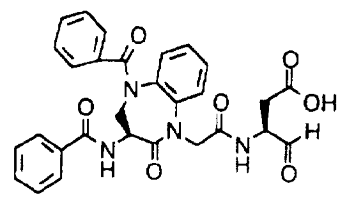
907b  ; and

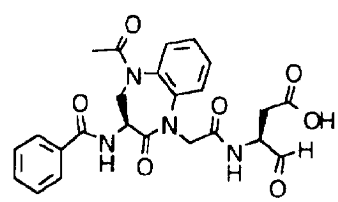
1029  .

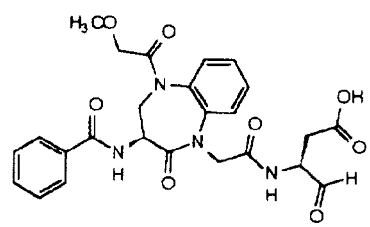
39. The compound according to claim 15 selected from the group consisting of:

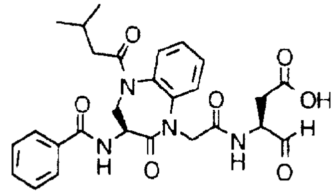
605a  ;

605b  ;

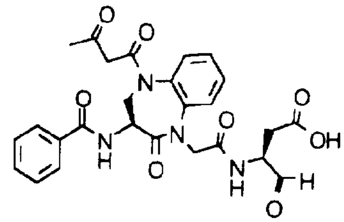
605c  ;

605d  ;

605e  ;

605f  ;

605g



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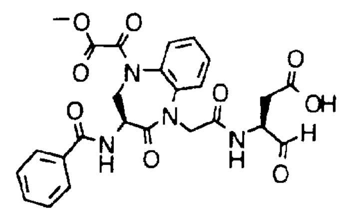
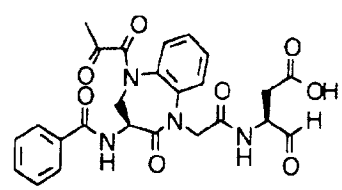
605h



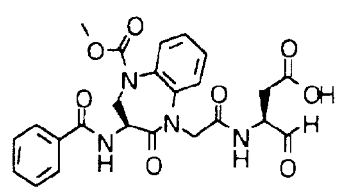
;

605i



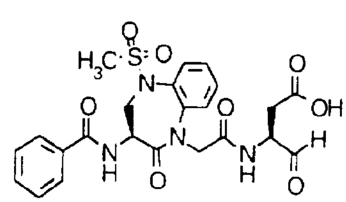
;

605j

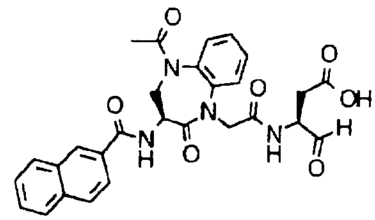


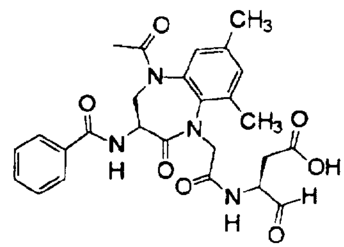
;

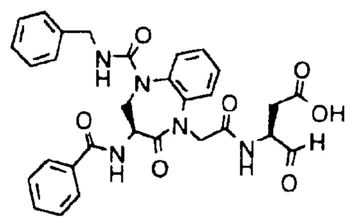
605m

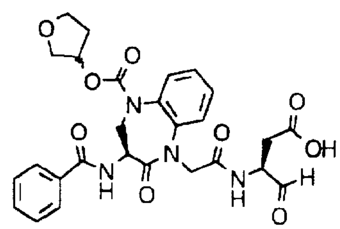


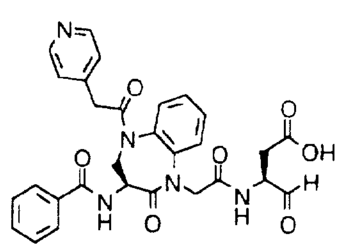
;

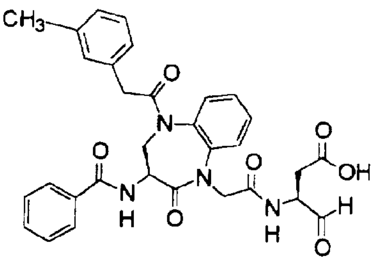
605n  ;

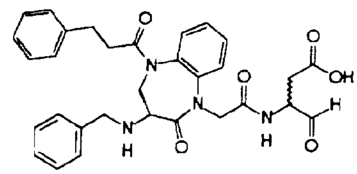
605o  ;

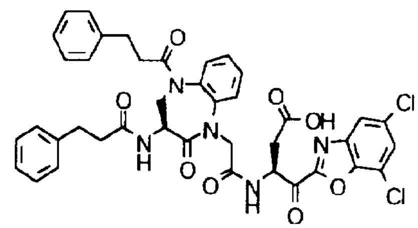
605p  ;

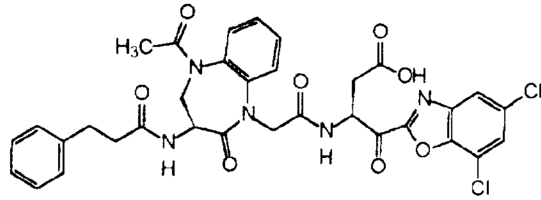
605q  ;

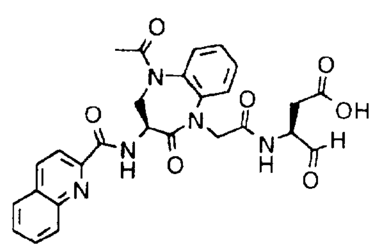
605s  ;

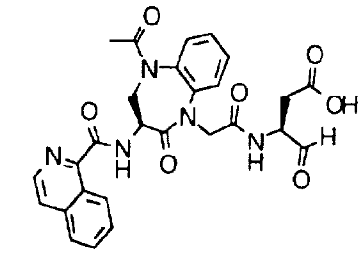
605t  ;

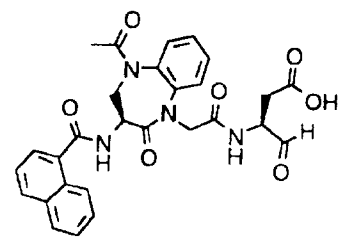
605v  ;

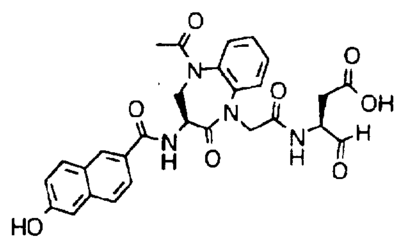
609a  ;

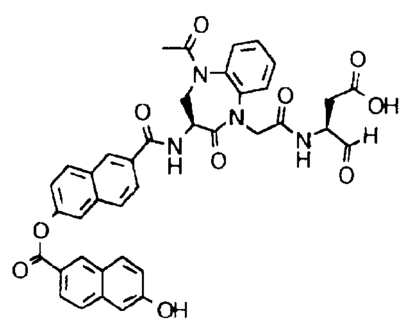
609b  ;

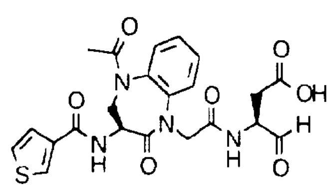
619  ;

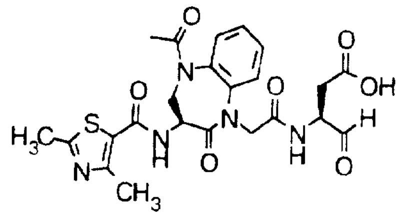
620  ;

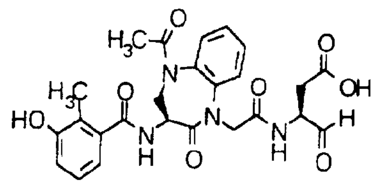
621  ;

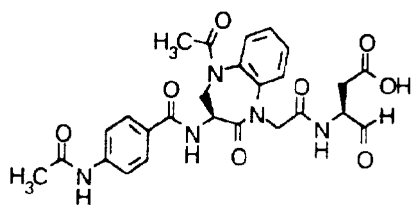
622  ;

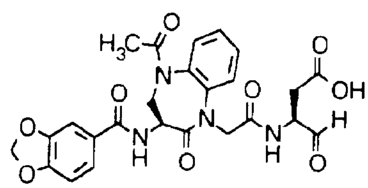
623  ;

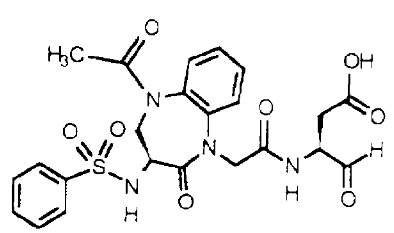
624  ;

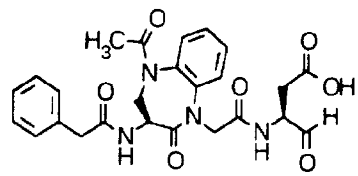
625  ;

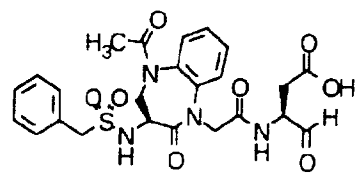
626  ;

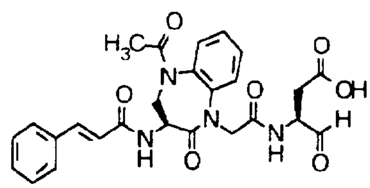
627  ;

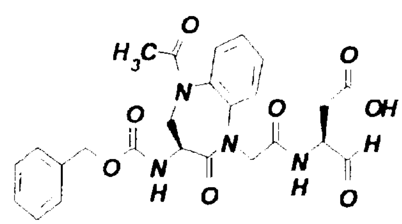
628  ;

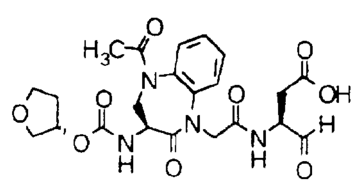
629  ;

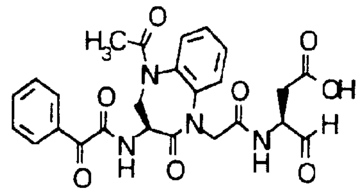
630  ;

631  ;

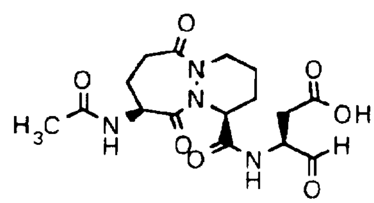
632  ;

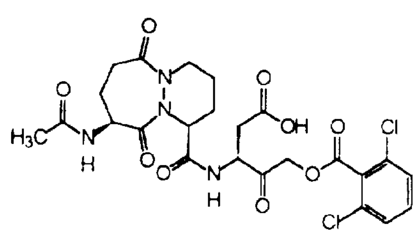
633  ;

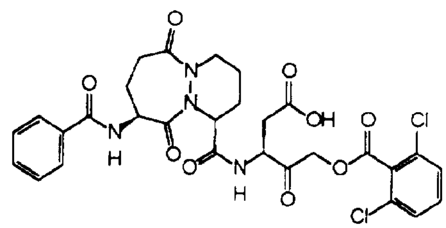
634  ; and

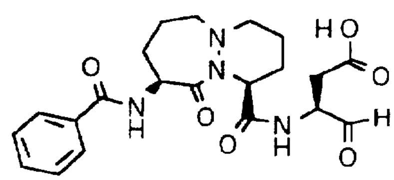
635  .

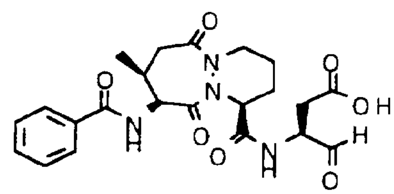
40. The compound according to claims 8 or 68, selected from the group consisting of:

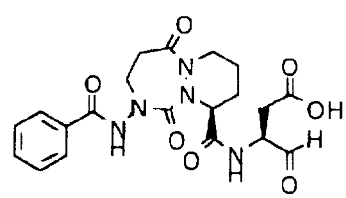
214c  ;

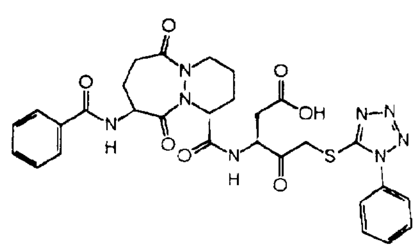
217c  ;

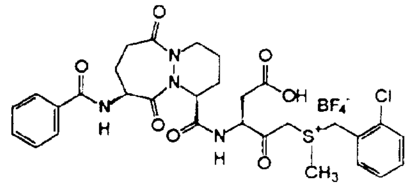
217e  ;

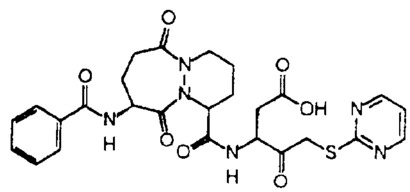
246  ;

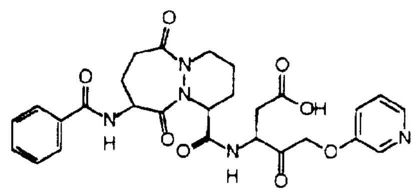
257  ;

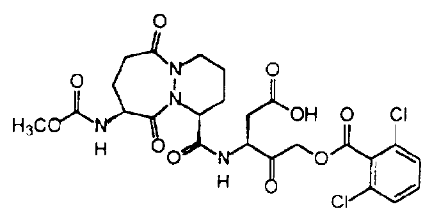
265  ;

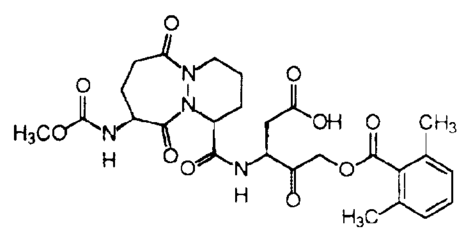
280  ;

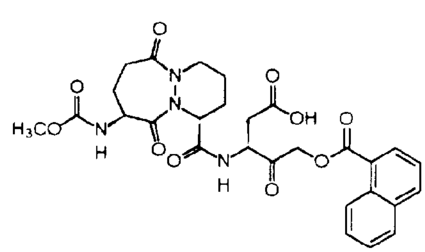
281  ;

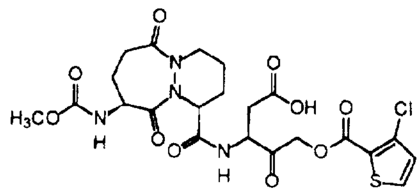
282  ;

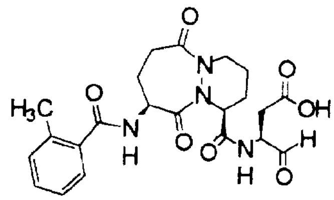
283  ;

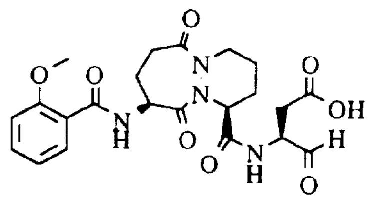
284  ;

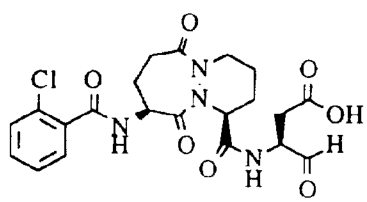
285  ;

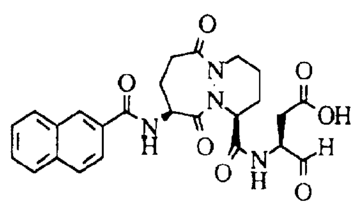
286  ;

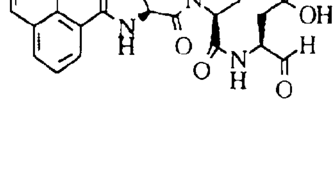
287  ;

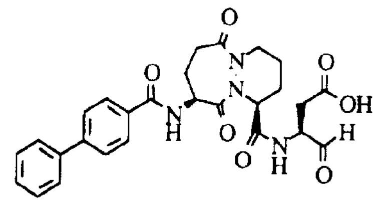
404  ;

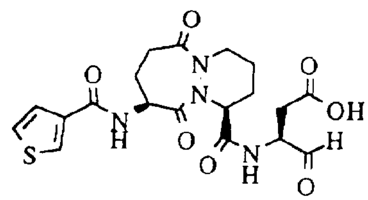
405  ;

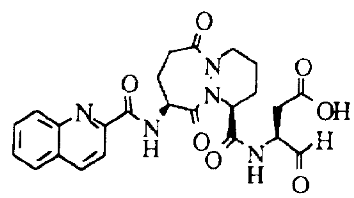
406  ;

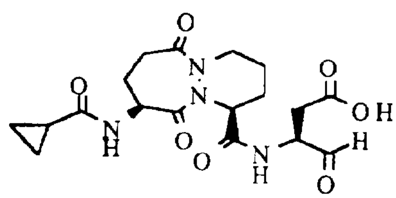
407  ;

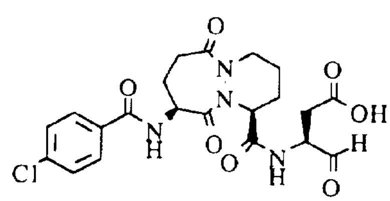
408  ;

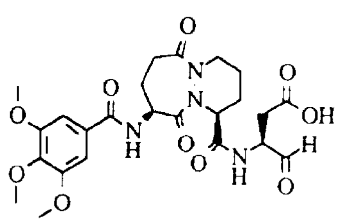
409  ;

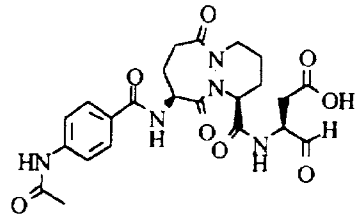
410  ;

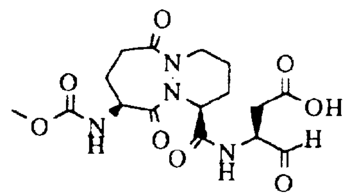
411  ;

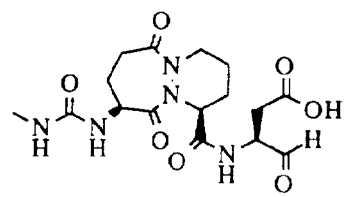
413  ;

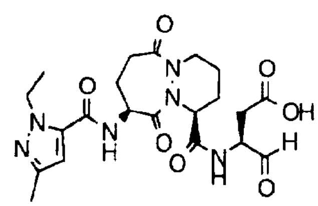
416  ;

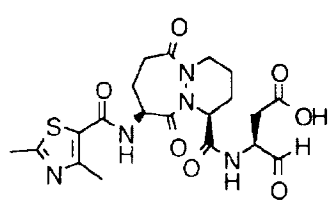
417  ;

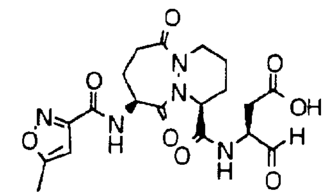
418  ;

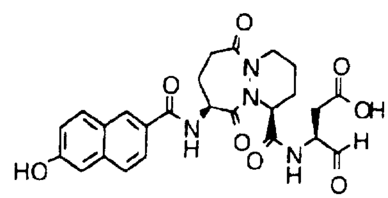
419  ;

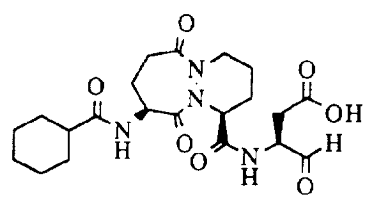
420  ;

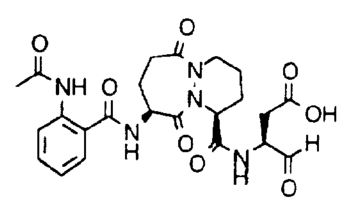
422  ;

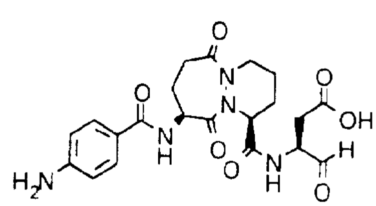
423  ;

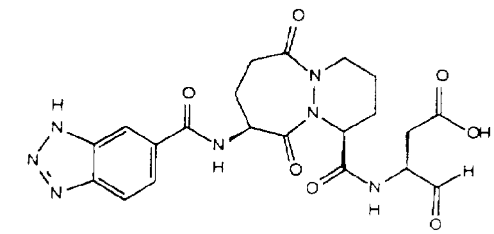
424  ;

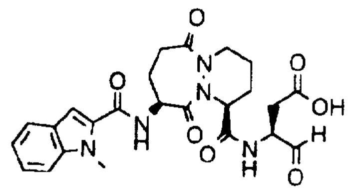
425  ;

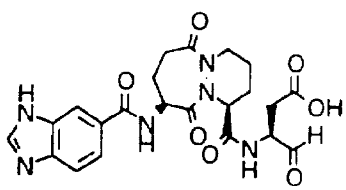
426  ;

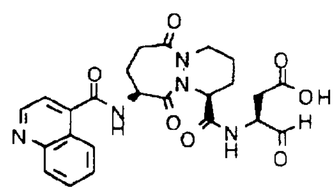
430  ;

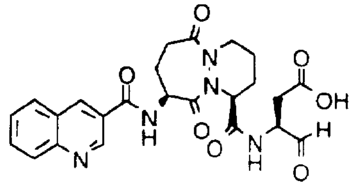
431  ;

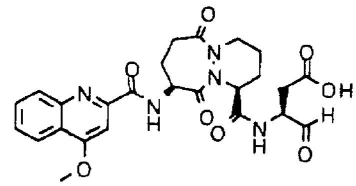
432  ;

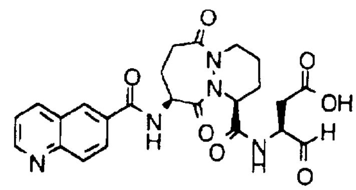
433  ;

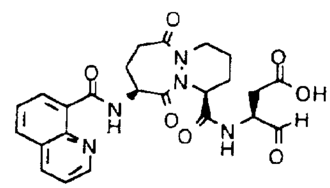
434  ;

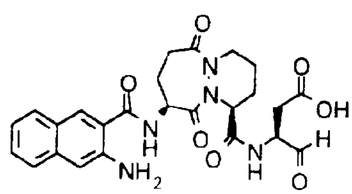
435  ;

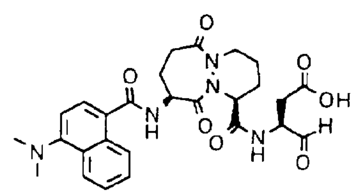
436  ;

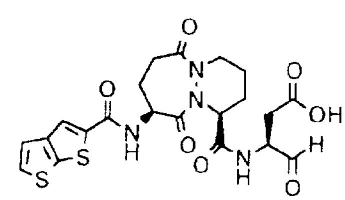
437  ;

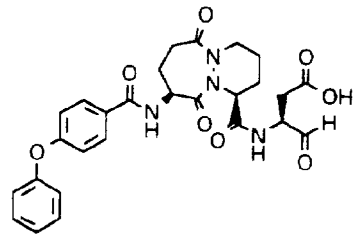
438  ;

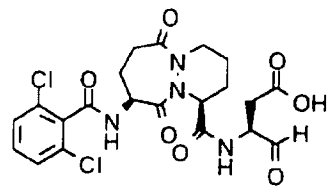
439  ;

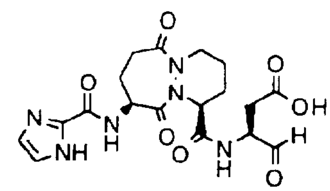
440  ;

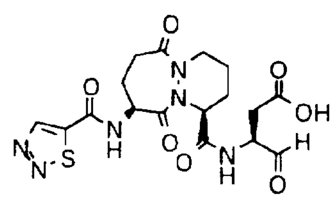
441  ;

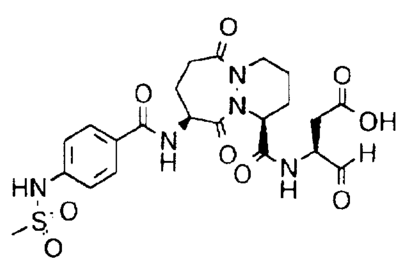
442  ;

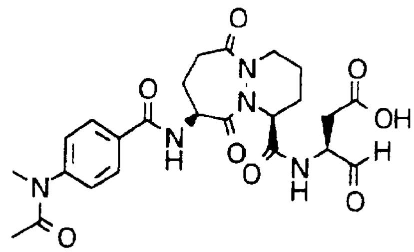
443  ;

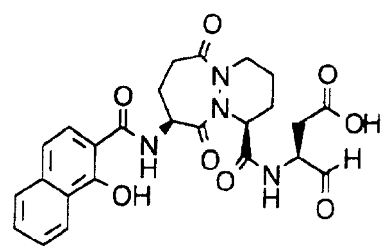
444  ;

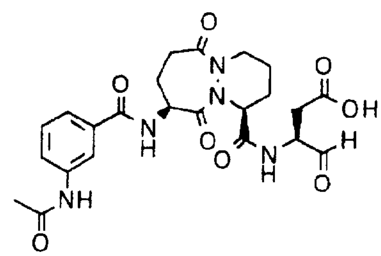
445  ;

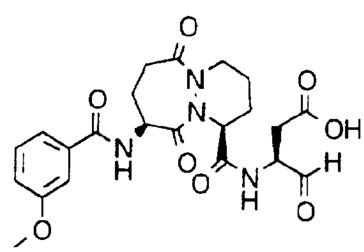
446  ;

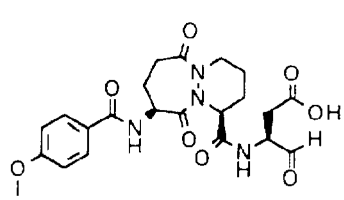
447  ;

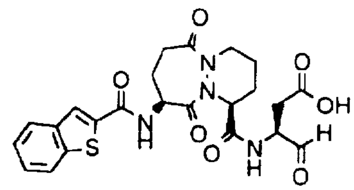
448  ;

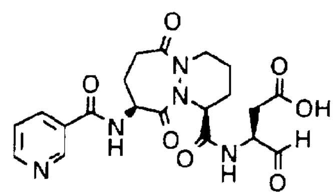
449  ;

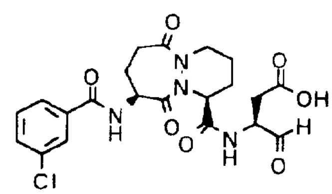
450  ;

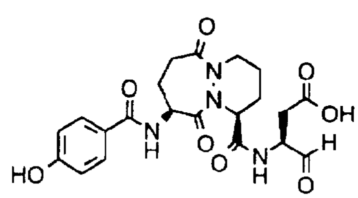
451  ;

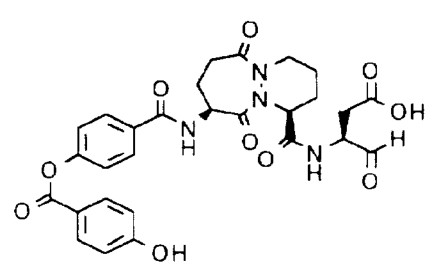
452  ;

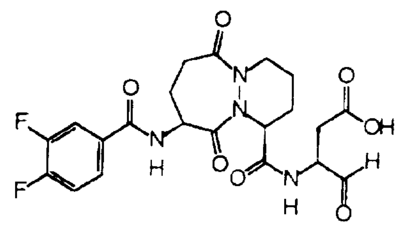
453  ;

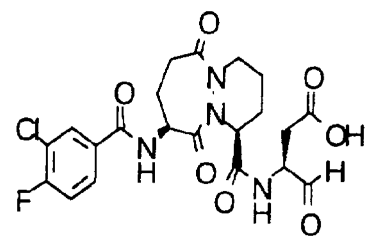
454  ;

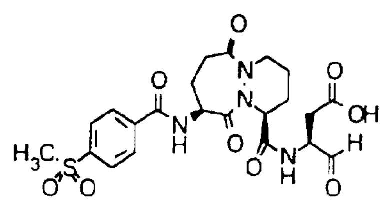
455  ;

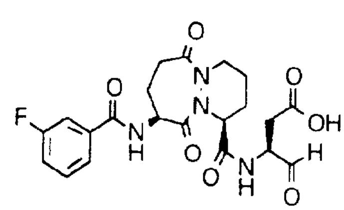
456  ;

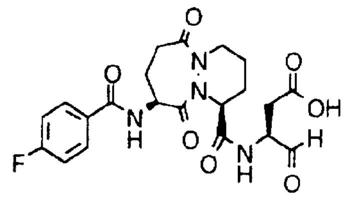
457  ;

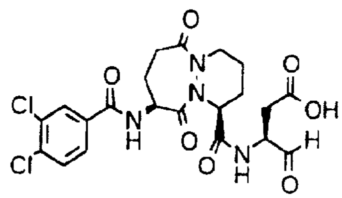
458  ;

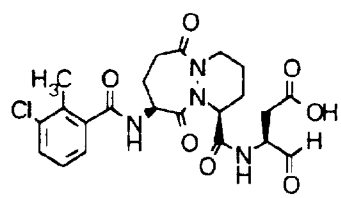
459  ;

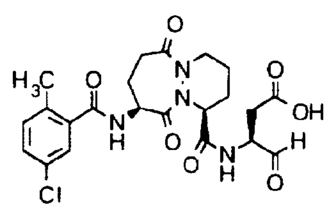
460  ;

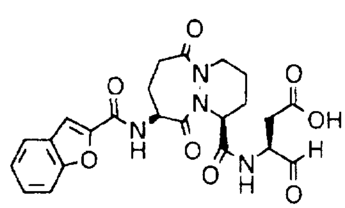
462  ;

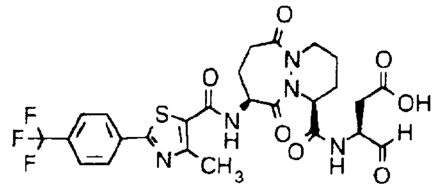
463  ;

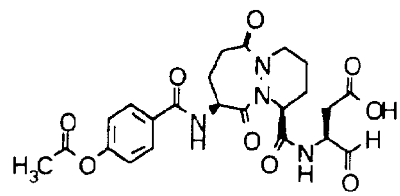
464  ;

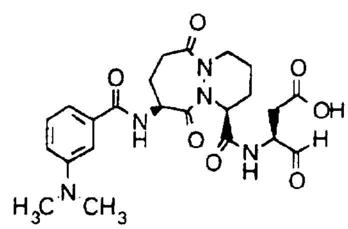
465  ;

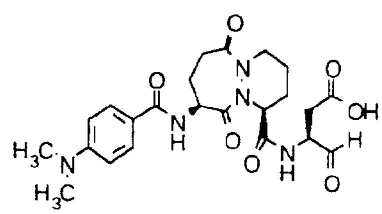
466  ;

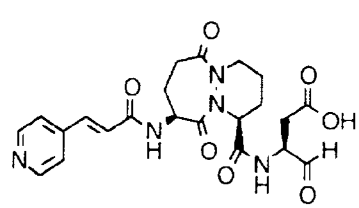
467  ;

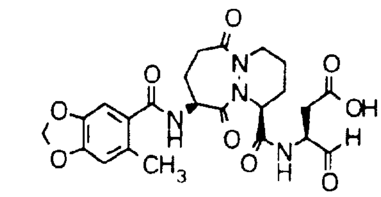
468  ;

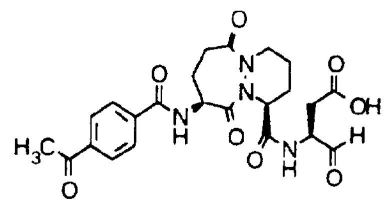
469  ;

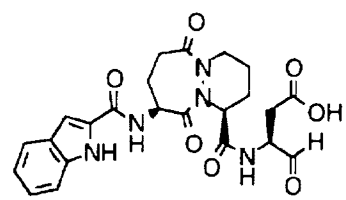
470  ;

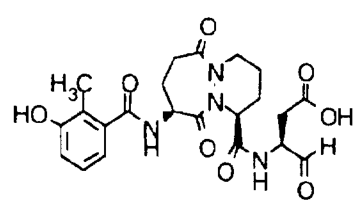
471  ;

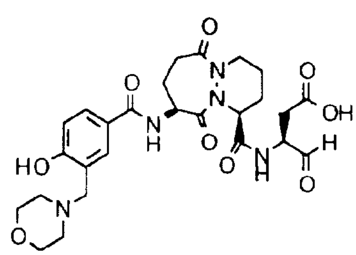
472  ;

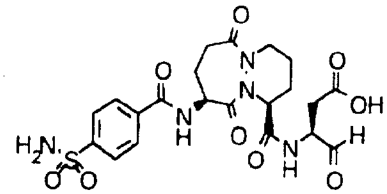
473  ;

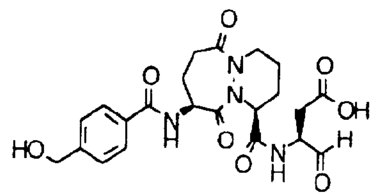
474  ;

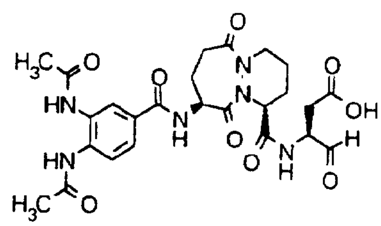
475  ;

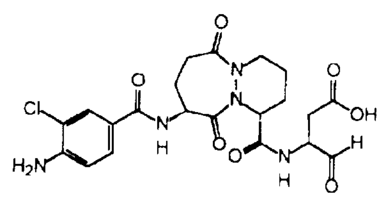
476  ;

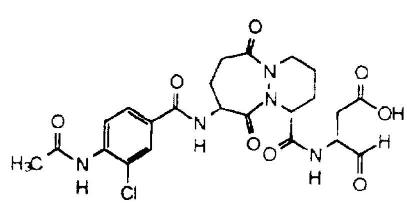
477  ;

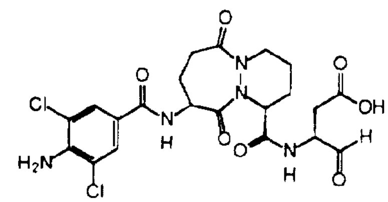
478  ;

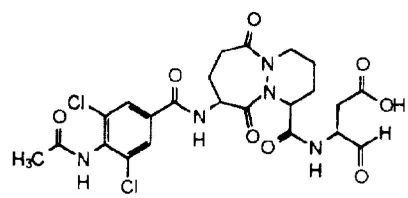
479  ;

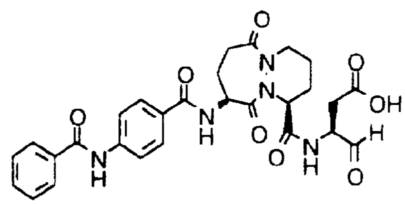
480  ;

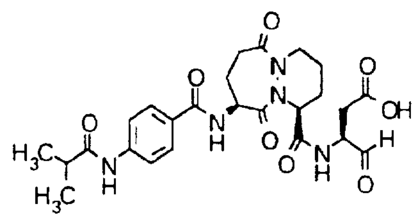
481  ;

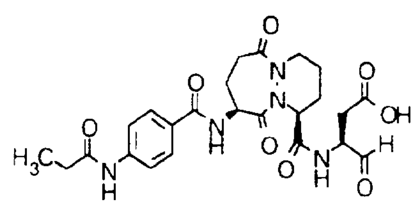
481s  ;

482  ;

482s  ;

483  ;

484  ;

485  ;

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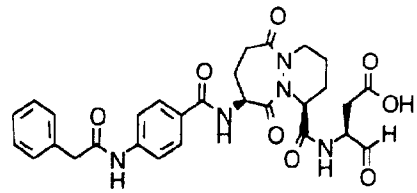

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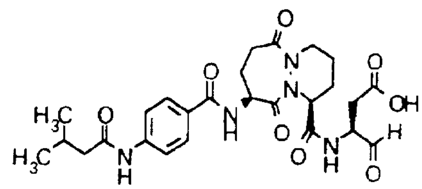

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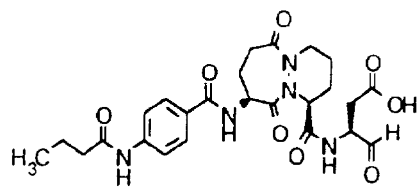

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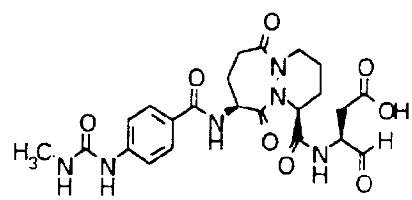

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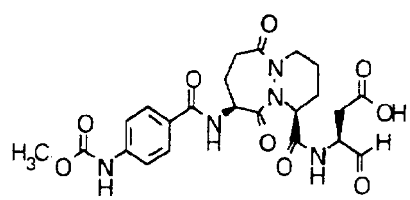

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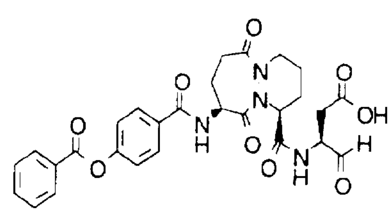

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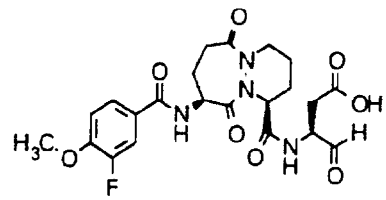
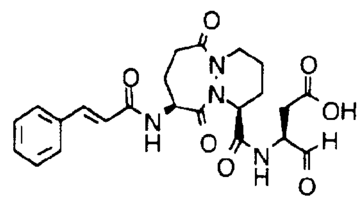
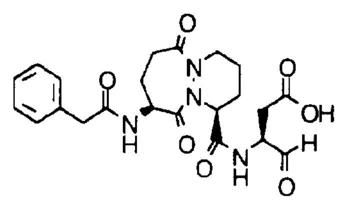
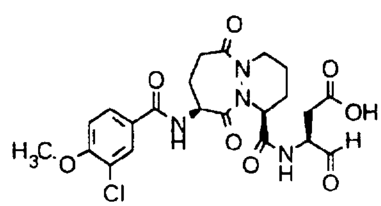
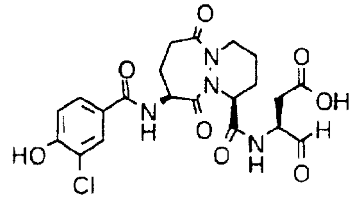
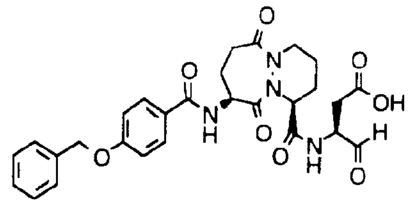
493  ;

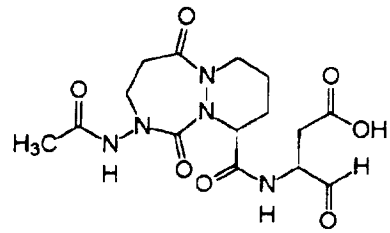
494  ;

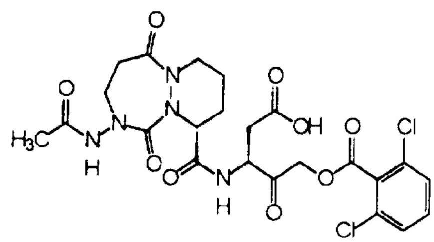
495  ;

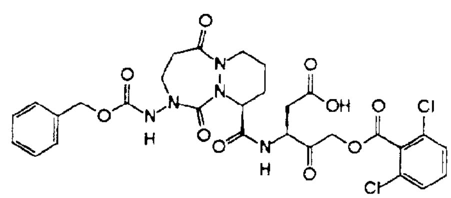
497  ;

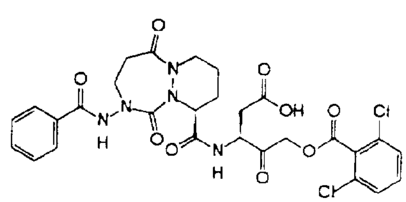
498  ;

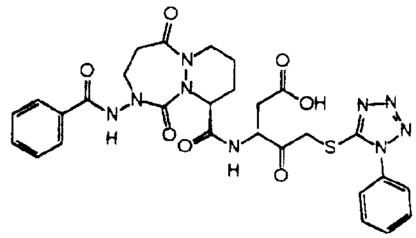
499  ;

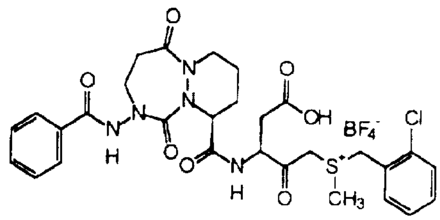
814c  ;

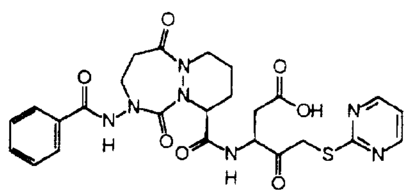
817c  ;

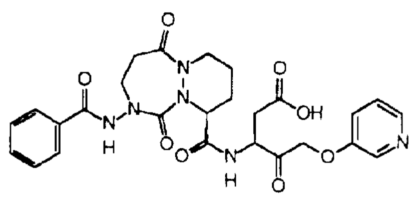
817d  ;

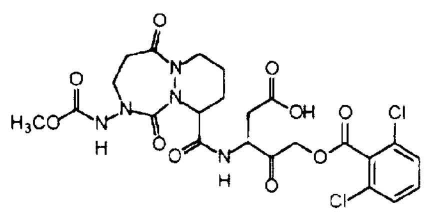
817e  ;

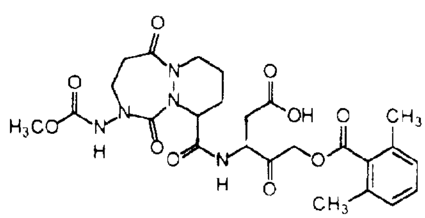
880  ;

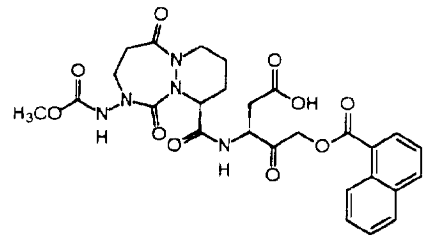
881  ;

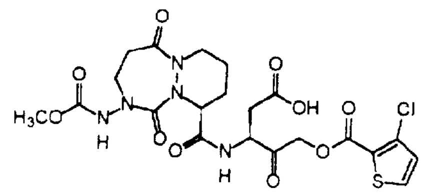
882  ;

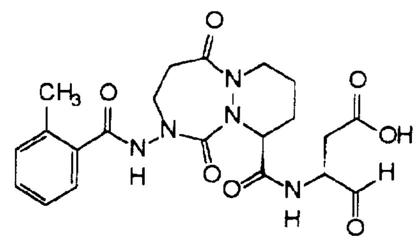
883  ;

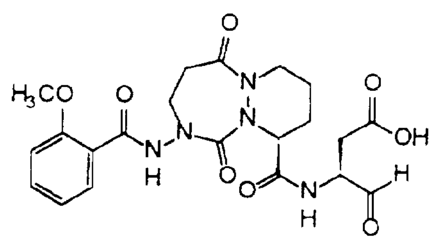
884  ;

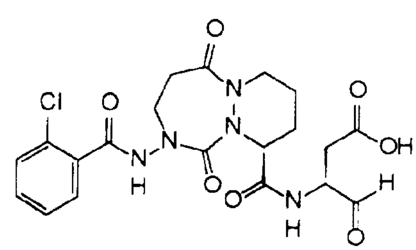
885  ;

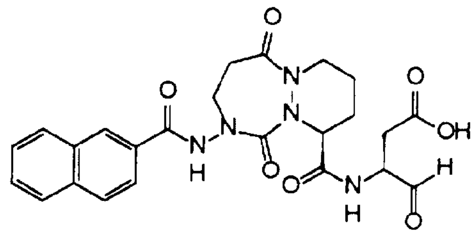
886  ;

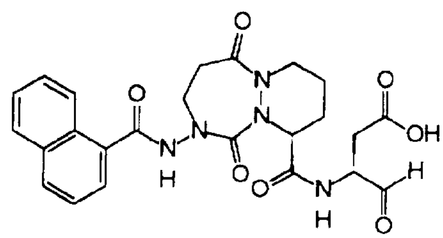
887  ;

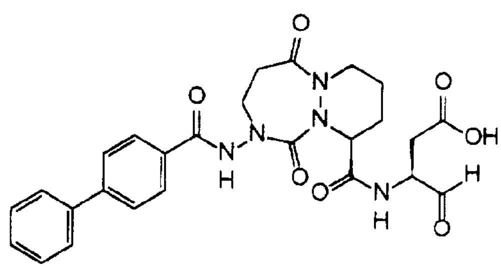
1004  ;

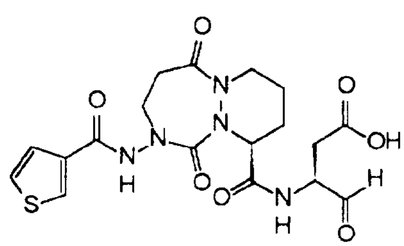
1005  ;

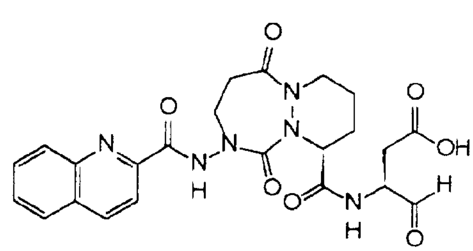
1006  ;

1007  ;

1008  ;

1009  ;

1010  ;

1011  ;

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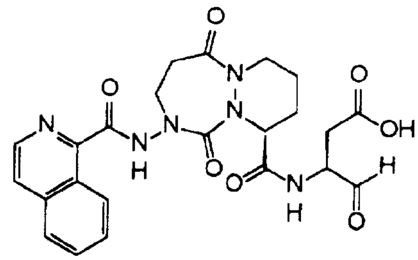

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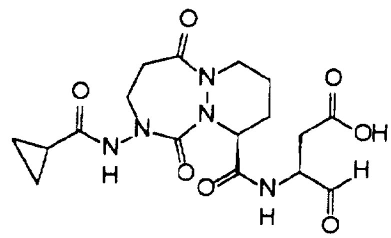

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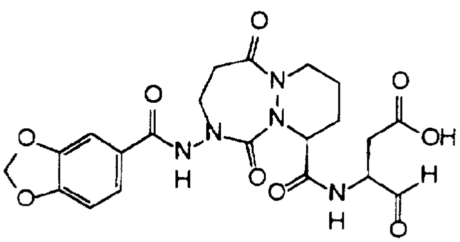

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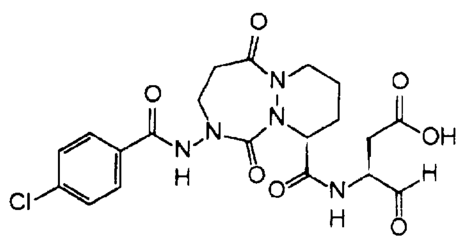

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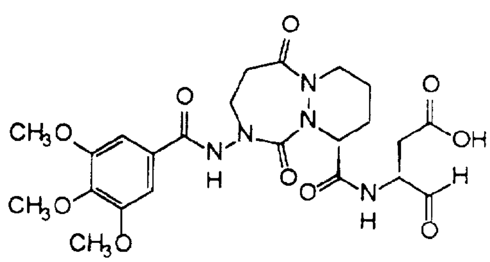

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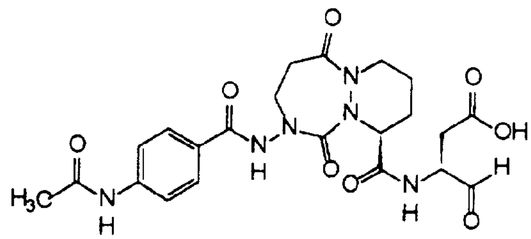

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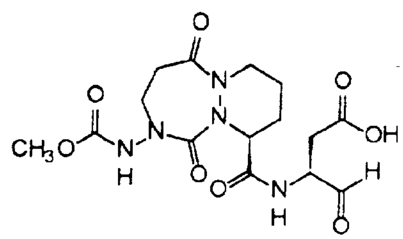

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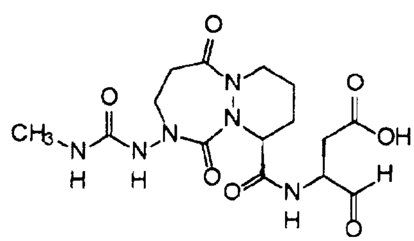

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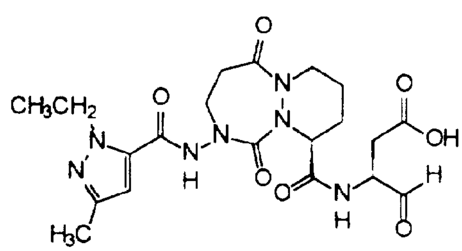

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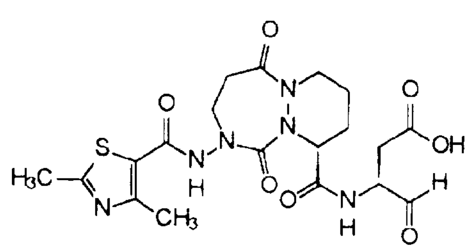

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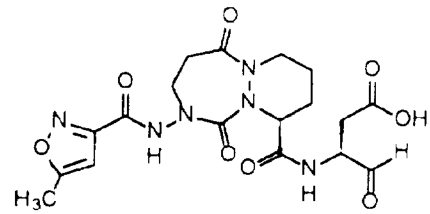
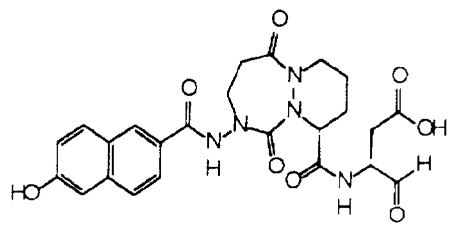
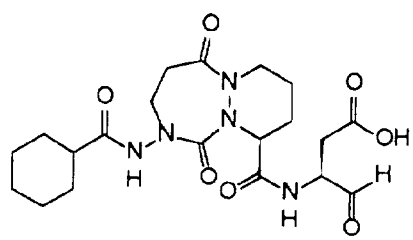
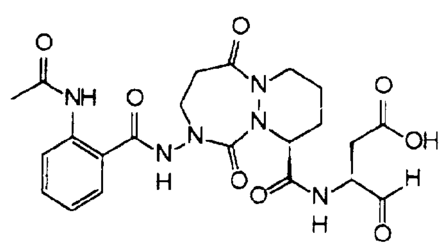
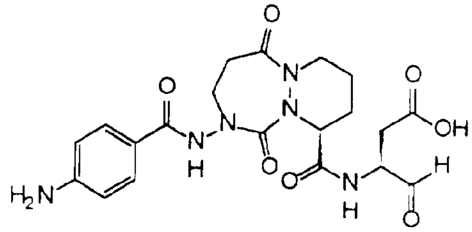
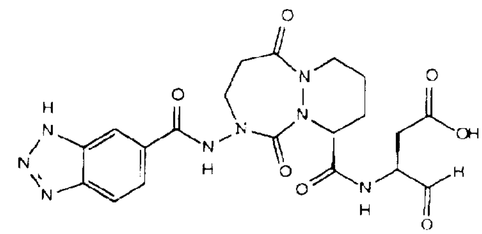
1024  ;

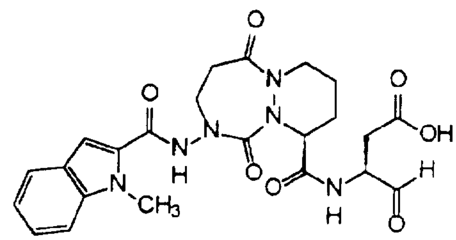
1025  ;

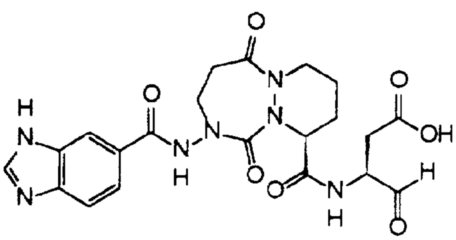
1026  ;

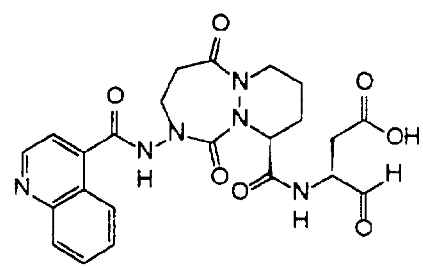
1030  ;

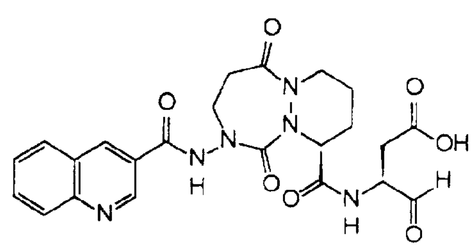
1031  ;

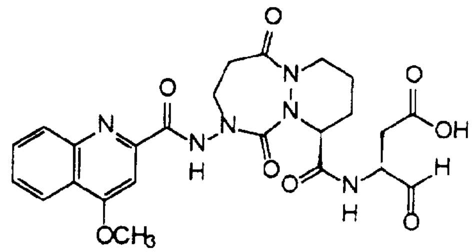
1032  ;

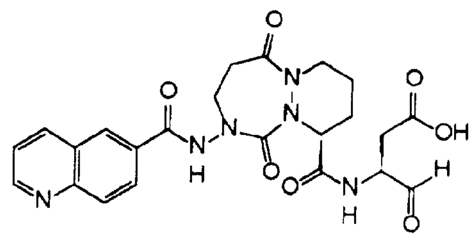
1033  ;

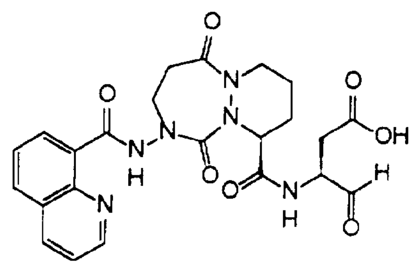
1034  ;

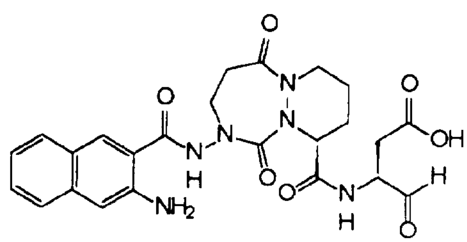
1035  ;

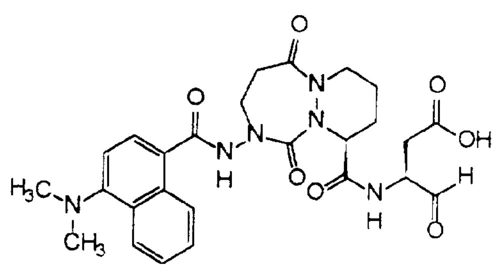
1036  ;

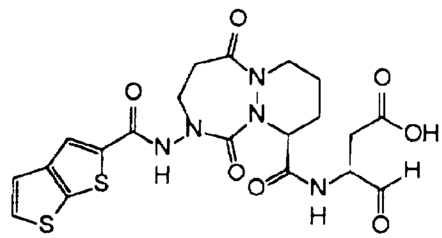
1037  ;

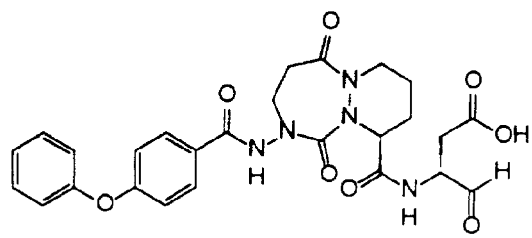
1038  ;

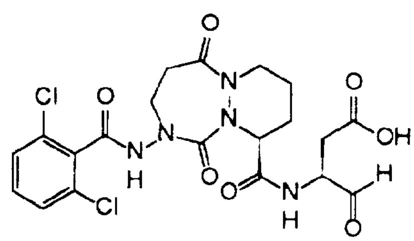
1039  ;

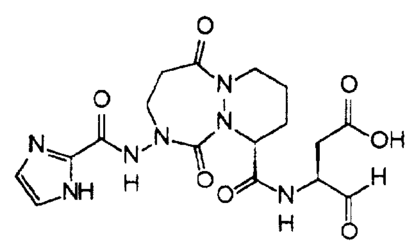
1040  ;

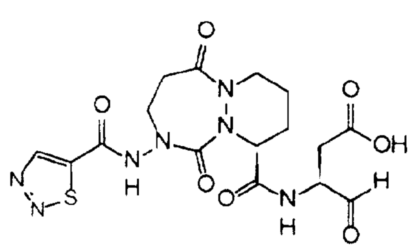
1041  ;

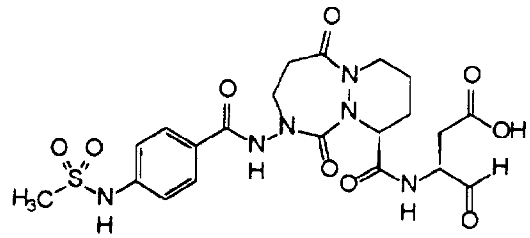
1042  ;

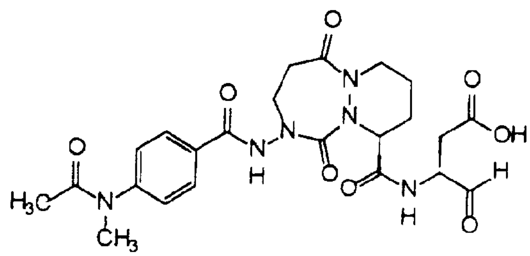
1043  ;

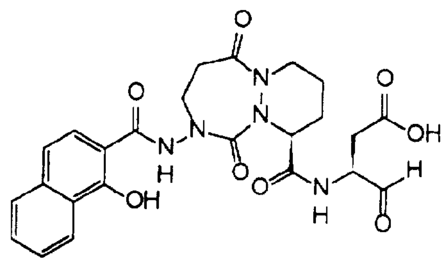
1044  ;

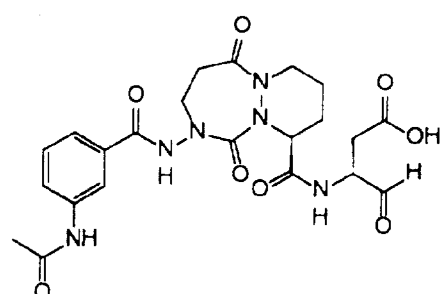
1045  ;

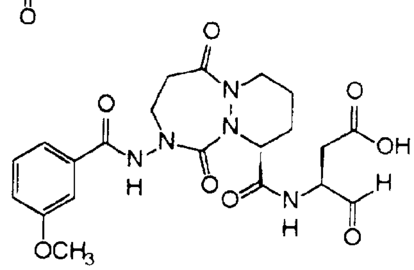
1046  ;

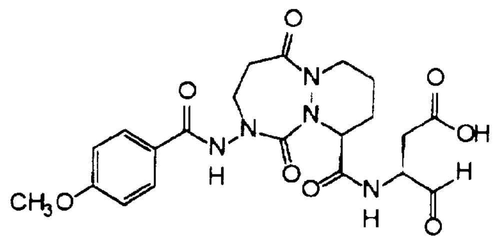
1047  ;

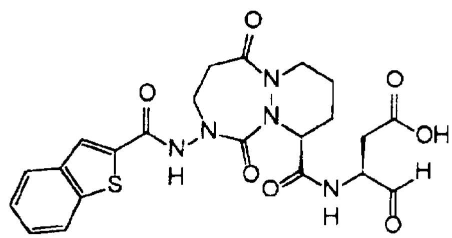
1048  ;

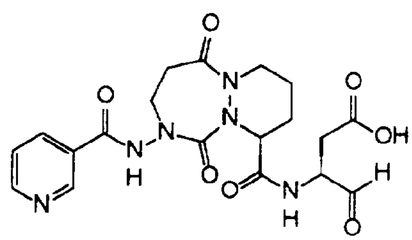
1049  ;

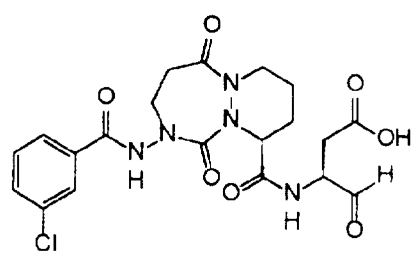
1050  ;

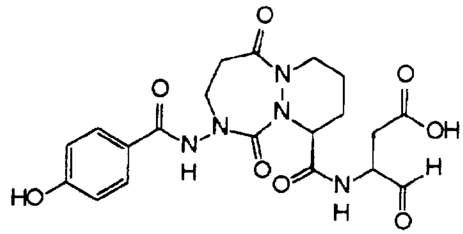
1051  ;

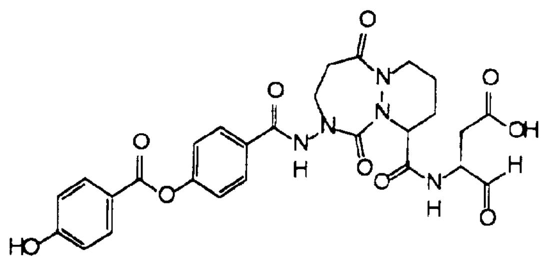
1052  ;

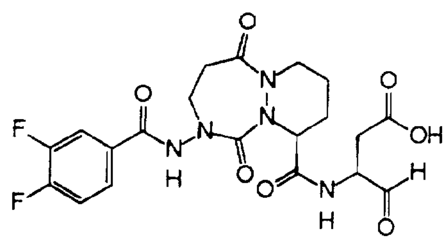
1053  ;

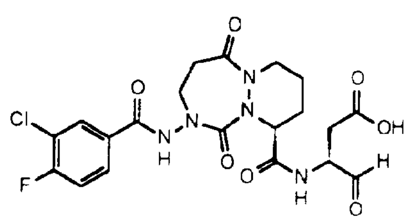
1054  ;

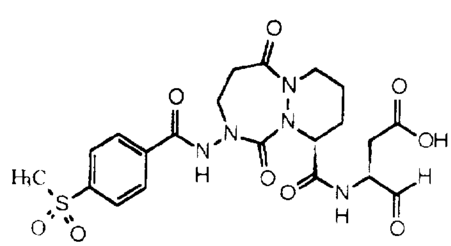
1055  ;

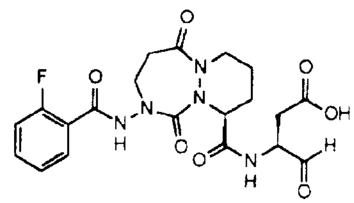
1056  ;

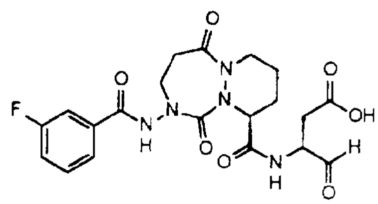
1057  ;

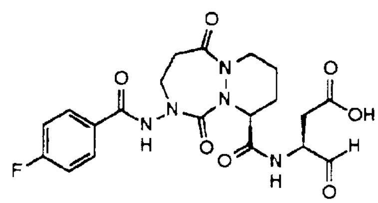
1058  ;

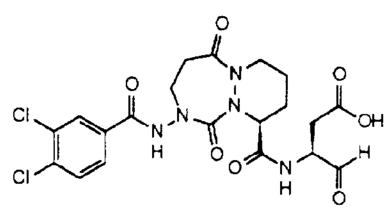
1059  ;

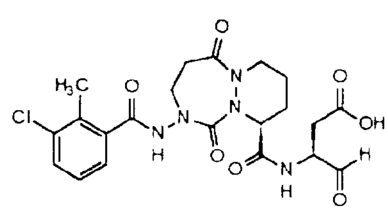
1060  ;

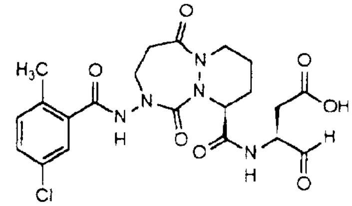
1061  ;

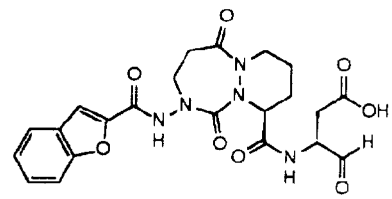
1062  ;

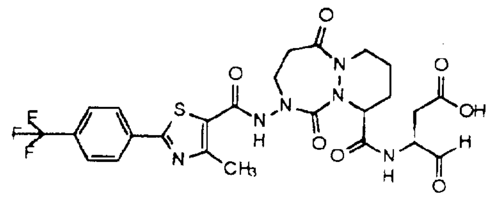
1063  ;

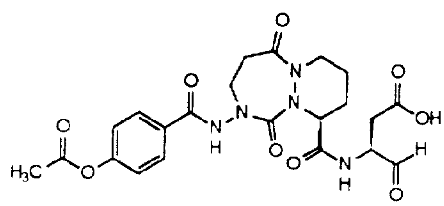
1064  ;

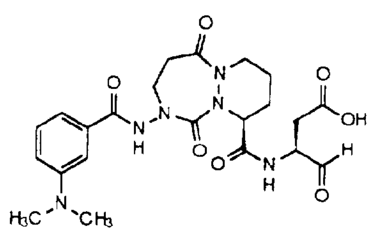
1065  ;

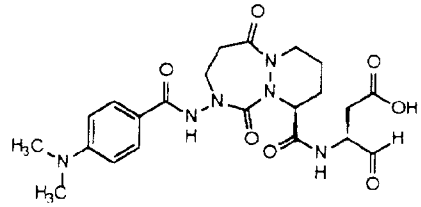
1066  ;

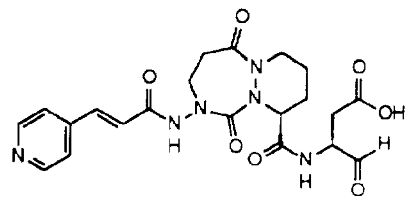
1067  ;

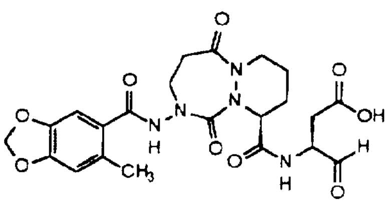
1068  ;

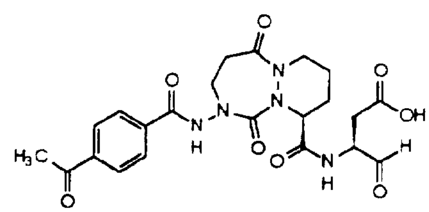
1069  ;

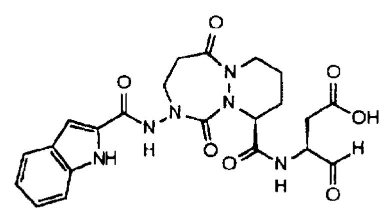
1070  ;

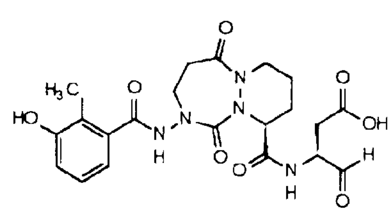
1071  ;

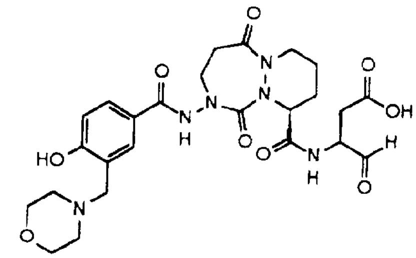
1072  ;

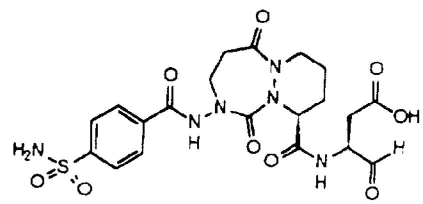
1073  ;

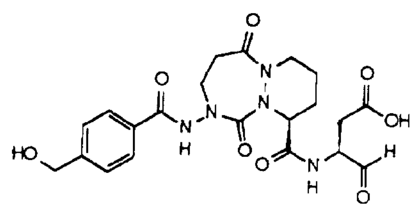
1074  ;

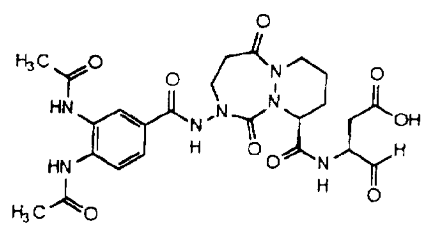
1075  ;

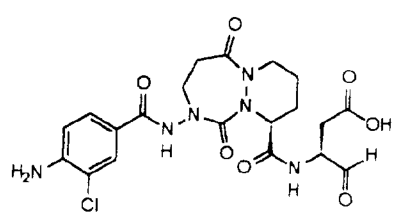
1076  ;

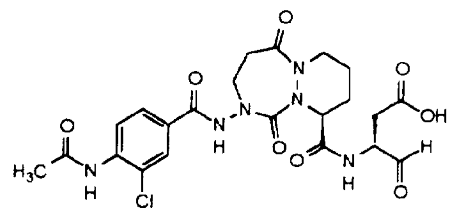
1077  ;

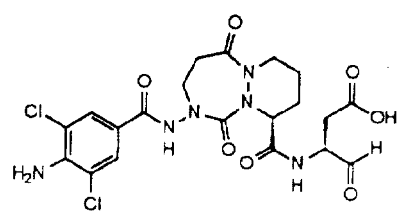
1078  ;

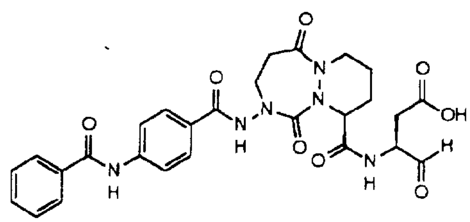
1079  ;

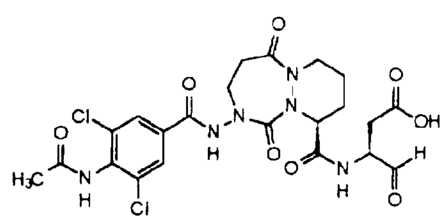
1080  ;

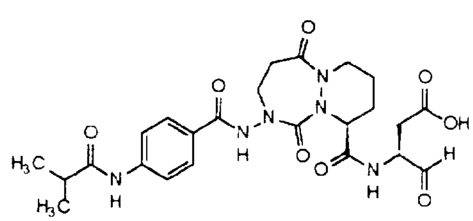
1081  ;

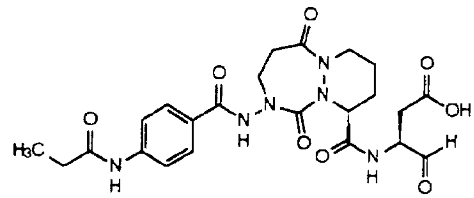
1081s  ;

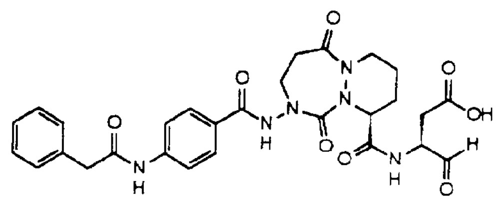
1082  ;

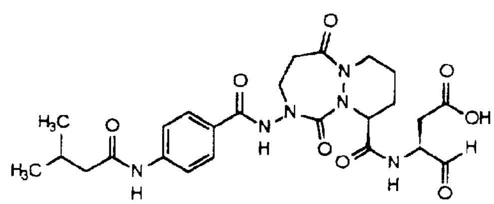
1083  ;

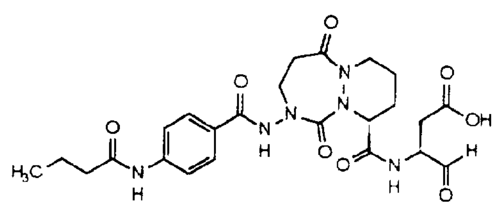
1082s  ;

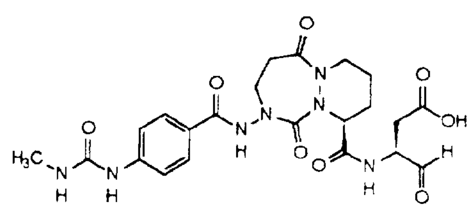
1084  ;

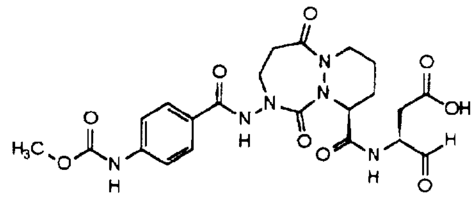
1085  ;

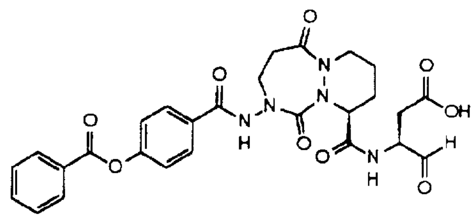
1086  ;

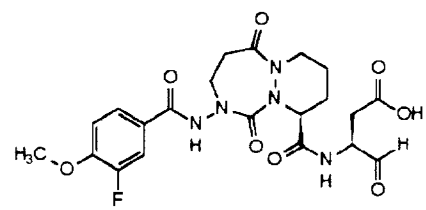
1087  ;

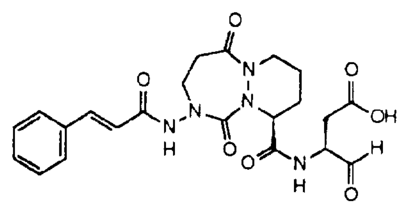
1088  ;

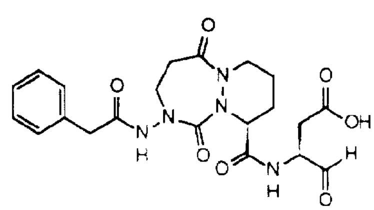
1089  ;

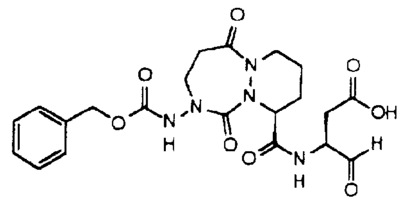
1090  ;

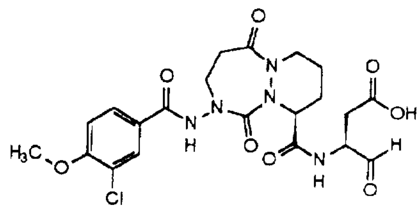
1091  ;

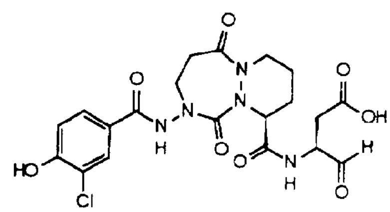
1093  ;

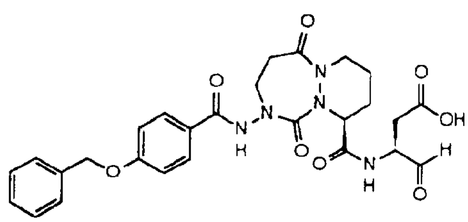
1094  ;

1095  ;

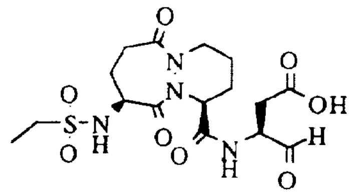
1096  ;

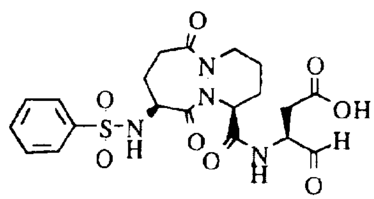
1097  ;

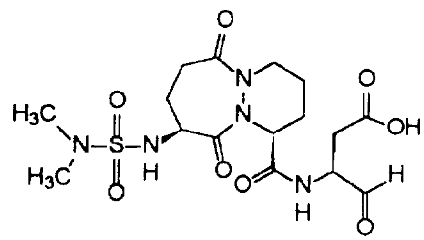
1098  ; and

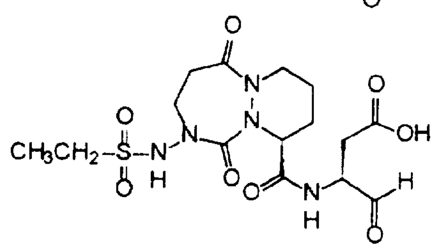
1099  .

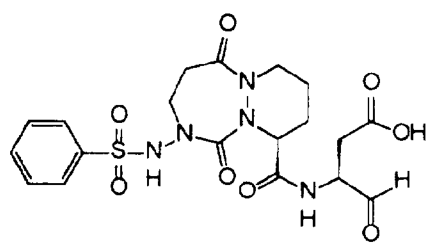
41. The compound according to claim 33 selected from the group consisting of:

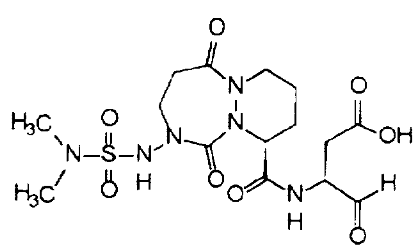
421  ;

427  ;

428  ;

1021  ;

1027  ; and

1028  .

42. A pharmaceutical composition comprising

an ICE inhibitor according to any one of claims 1-41 and 57-135 in an amount effective for treating or preventing an IL-1-mediated disease and a pharmaceutically acceptable carrier.

43. A pharmaceutical composition comprising an ICE inhibitor according to any one of claims 1-41 and 57-135 in an amount effective for treating or preventing an apoptosis-mediated disease and a pharmaceutically acceptable carrier.

44. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is an inflammatory disease selected from the group consisting of osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, and adult respiratory distress syndrome.

45. The pharmaceutical composition according to claim 44, wherein the inflammatory disease is osteoarthritis or acute pancreatitis.

46. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is an autoimmune disease selected from the group consisting of glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, and graft vs host disease.

47. The pharmaceutical composition according to claim 46, wherein the autoimmune disease is rheumatoid arthritis, inflammatory bowel disease, or Crohn's disease, or psoriasis.

48. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a destructive bone disorder selected from the group consisting of osteoporosis or multiple myeloma-related bone disorder.

49. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a proliferative disorder selected from the group consisting of acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

50. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is an infectious disease, selected from the group consisting of sepsis, septic shock, and Shigellosis.

51. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a degenerative or necrotic disease, selected from the group consisting of Alzheimer's disease, Parkinson's disease, cerebral ischemia, and myocardial ischemia.

52. The pharmaceutical composition according to claim 51, wherein the degenerative disease is Alzheimer's disease.

53. The pharmaceutical composition according

to claim 43, wherein the apoptosis-mediated disease is a degenerative disease, selected from the group consisting of Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

54. A pharmaceutical composition for inhibiting an ICE-mediated function comprising an ICE inhibitor according to any one of claims 1-41 and 57-135 and a pharmaceutically acceptable carrier.

55. A method for treating or preventing a disease selected from the group consisting of an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a necrotic disease, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular

atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke in a patient comprising the step of administering to said patient a pharmaceutical composition according to any one of claims 42 to 54.

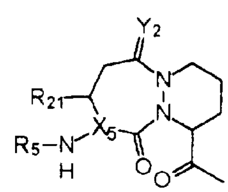
56. The method according to claim 55, wherein the disease is selected from the group consisting of osteoarthritis, acute pancreatitis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, psoriasis, and Alzeheimer's disease.

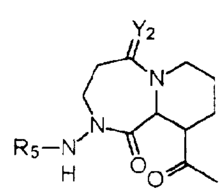
57. A compound represented by the formula:

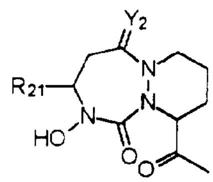
$$\text{(III)} \qquad R_1\text{-}\underset{\displaystyle H}{\underset{|}{N}}\text{-}R_2$$

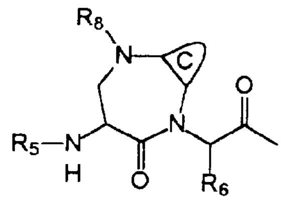
wherein:

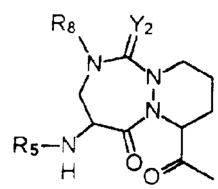
R_1 is selected from the group consisting of the following formulae:

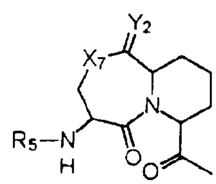
(e10)  ;

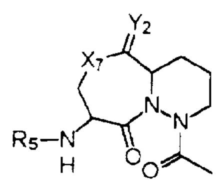
(e11)  ;

(e12)  ;

(w2)  ;

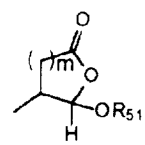
(y1)  ;

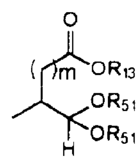
(y2)  ;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_2 is:

(a)  , or

(b)  ;

m is 1 or 2;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$-C(O)-N(R_{10})(R_{10})$

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-CH_2-O-R_9$,

$-C(O)C(O)-R_{10}$,

$-R_9$,

$-H$,

$-C(O)C(O)-OR_{10}$, and

$-C(O)C(O)-N(R_9)(R_{10})$;

X_5 is CH or N;

Y_2 is H_2 or O;

X_7 is $-N(R_8)-$ or $-O-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(H)-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$;
$-C(O)-CH_2N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
$-H$, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9, $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

```
 O
/ \
   CH2,
\ /
 O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

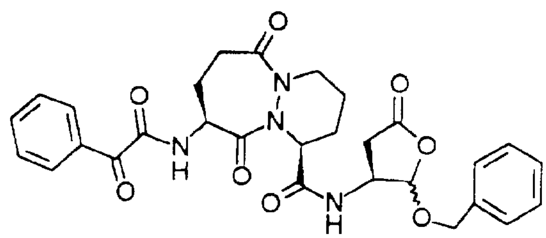
58. The compound according to claim 57, wherein R_1 is (w2).

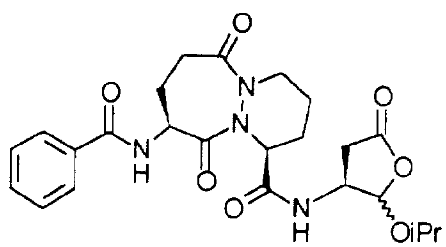
59. The compound according to claim 57,

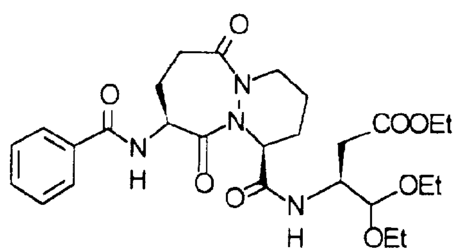
wherein R_1 is (e10) and X_5 is CH.

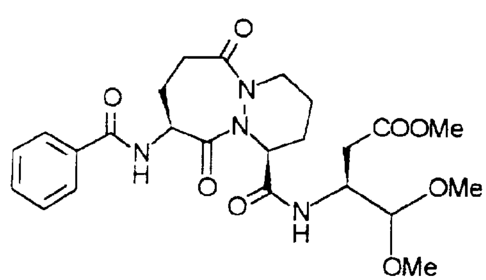
60. The compound according to claim 57, wherein R_1 is (e10) and X_5 is N.

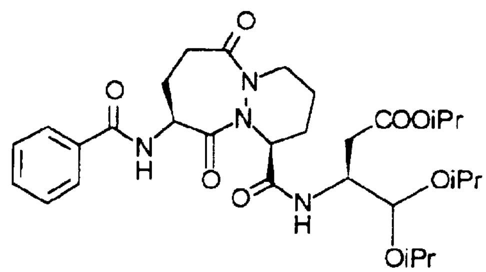
61. The compound according to claim 57, selected from the group consisting of:

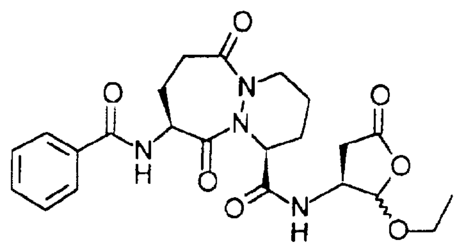
2001  ;

2100a  ;

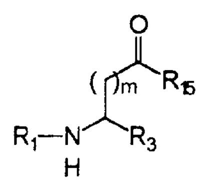
2100b  ;

2100c  ;

2100d  ; and

2100e  .

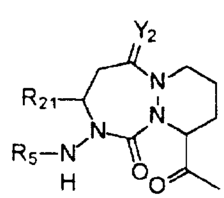
62. A compound represented by the formula:

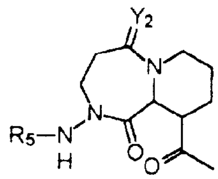
(IV) 

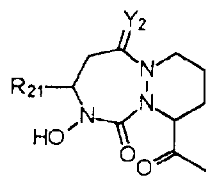
wherein:

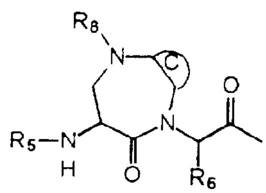
m is 1 or 2;

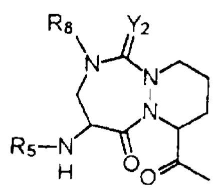
R_1 is selected from the group consisting of the following formulae:

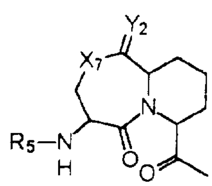
(e10-A)  ;

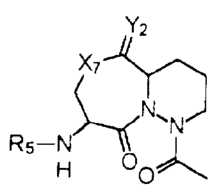
(e11)  ;

(e12)  ;

(w2)  ;

(y1)  ;

(y2)  ; and

(z)  ;

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,

cyclopentyl, and cyclohexyl;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

$-C(O)-CH_2-T_1-R_{11}$,

$-C(O)-CH_2-F$,

$-C=N-O-R_9$, and

$-CO-Ar_2$;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$-C(O)-N(R_{10})(R_{10})$

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-CH_2-O-R_9$,

$-C(O)C(O)-R_{10}$,

$-R_9$,

-H,

$-C(O)C(O)-OR_{10}$, and

$-C(O)C(O)-N(R_9)(R_{10})$;

Y_2 is H_2 or O;

X_7 is $-N(R_8)-$ or -O-;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

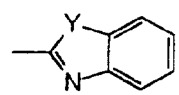
each R_{11} is independently selected from the group consisting of:
$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and
$-C(O)-Ar_4$;

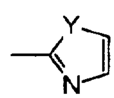
R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with

-Ar_3, -$CONH_2$, -OR_5, -OH, -OR_9, or -CO_2H;

each R_{21} is independently selected from the group consisting of -H or a -C_{1-6} straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q_1 or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Ar_4 is a cyclic group independently selected

from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group consisting of -NH_2, -CO_2H, -Cl, -F, -Br, -I, -NO_2, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, -OR_5, -NHR_5, -OR_9, -N(R_9)(R_{10}), -R_9, -C(O)-R_{10}, and

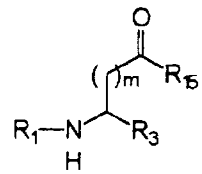
```
 O
/ \
   CH2;
\ /
 O
```

provided that when -Ar_3 is substituted with a Q_1 group which comprises one or more additional -Ar_3 groups, said additional -Ar_3 groups are not substituted with another -Ar_3.

63. The compound according to claim 62, wherein R_1 is (w2).

64. The compound according to claim 62, wherein R_1 is (e10-A).

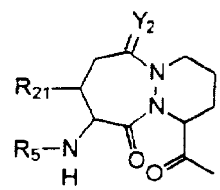
65. A compound represented by the formula:

(V) 

wherein:

m is 1 or 2;

R_1 is:

(e10-B)  ;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

$-C(O)-CH_2-T_1-R_{11}$,

$-C(O)-CH_2-F$,

$-C=N-O-R_9$, and

$-CO-Ar_2$;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$-C(O)-N(R_{10})(R_{10})$

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-CH_2-O-R_9$,

$-C(O)C(O)-R_{10}$,

$-R_9$,

-H,

$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

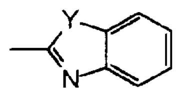
$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and
$-C(O)-Ar_4$;

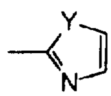
R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

R_{21} is $-CH_3$;

Ar_2 is independently selected from the following

group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally

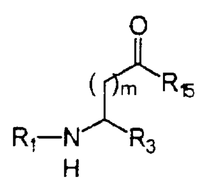
containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

```
 O
/ \
   CH2;
\ /
 O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

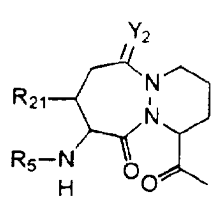
66. A compound represented by the formula:

(V) 

wherein:

m is 1 or 2;

R_1 is:

(e10-B)  ;

R_3 is selected from the group consisting of:

-CN,

$-C(O)-H$,
$-C(O)-CH_2-T_1-R_{11}$,
$-C(O)-CH_2-F$,
$-C{=}N-O-R_9$, and
$-CO-Ar_2$;

each R_5 is $-C(O)C(O)-OR_{10}$;

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

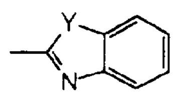
each R_{11} is independently selected from the group consisting of:
$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and
$-C(O)-Ar_4$;

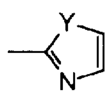
R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with

$-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected

from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

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 O
/ \
   CH2;
\ /
 O
```
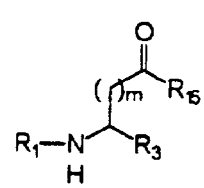

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

67. The compound according to claim 66, wherein R_{21} is $-CH_3$.

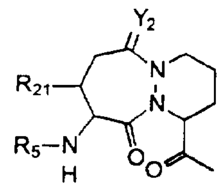
68. A compound represented by the formula:

(V) 

wherein:

m is 1 or 2;

R_1 is:

(e10-B) 

;

R_3 is selected from the group consisting of:

-CN,
-C(O)-H,
-C(O)-CH_2-T_1-R_{11},
-C(O)-CH_2-F,
-C=N-O-R_9, and
-CO-Ar_2;

each R_5 is independently selected from the group consisting of:

-C(O)-R_{10},
-C(O)O-R_9,
-C(O)-N(R_{10})(R_{10})
-S(O)$_2$-R_9,
-S(O)$_2$-NH-R_{10},
-C(O)-CH_2-O-R_9,
-C(O)C(O)-R_{10},
-R_9,
-H,
-C(O)C(O)-OR_{10}, and
-C(O)C(O)-N(R_9)(R_{10});

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

$-Ar_4$,

$-(CH_2)_{1-3}-Ar_4$,

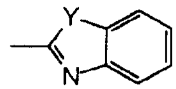
-H, and

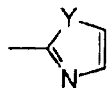
$-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

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  O
 / \
    CH2;
 \ /
  O
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provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$;

provided that when:

m is 1;
R_{15} is -OH;
R_{21} is -H; and

Y_2 is O and R_3 is -C(O)-H, then R_5 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$, 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

-H;

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl,4-(carboxyethylthio)phenyl,

4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$, wherein R_9 is isobutyl or $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl;

and when R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl or 5-(1-(4-chloro-2-pyridinyl)-3-trifluoromethyl)pyrazolyl, then R_5 cannot be:

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl;

and when R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, or

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methyl)phenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benztriazolyl, N-carboethoxy-5-benztriazolyl, N-carboethoxy-5-benzimidazolyl, or

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$,; and when

Y_2 is H_2, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11}

is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl.

69. The compound according to claim 68, wherein R_{21} is $-CH_3$.

70. The compound according to claim 68, wherein R_5 is $-C(O)-C(O)-OR_{10}$.

71. The compound according to claim 68, wherein R_5 is $-C(O)-C(O)-OR_{10}$ and R_{21} is $-CH_3$.

72. The compound according to any one of claims 66, 67, 70 and 71, wherein R_3 is $-C(O)-H$.

73. The compound according to any one of claims 65, 68 and 69, wherein R_3 is $-C(O)-H$.

74. The compound according to claim 68, wherein:

R_3 is $-C(O)-H$, and

R_5 is $-C(O)-R_{10}$, wherein:

R_{10} is Ar_3, wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

$-F$,

$-Cl$,

$-N(H)-R_5$, wherein $-R_5$ is $-H$ or $-C(O)-R_{10}$, wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein Ar_3 is

phenyl,

$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a $-C_{1-4}$ straight or branched alkyl group, or

$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or branched alkyl group.

75. The compound according to claim 74, wherein Ar_3 is phenyl being optionally singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by $-NH-R_5$, $-N(R_9)(R_{10})$, or $-O-R_5$.

76. The compound according to claim 68, wherein:

R_3 is -C(O)-H;

R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

77. The compound according to claim 68, wherein:

R_3 is -C(O)-H; and

R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

78. The compound according to claim 68, wherein:

R_3 is -C(O)-H; and

R_5 is -C(O)-R_{10}, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is phenyl, substituted by

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 O
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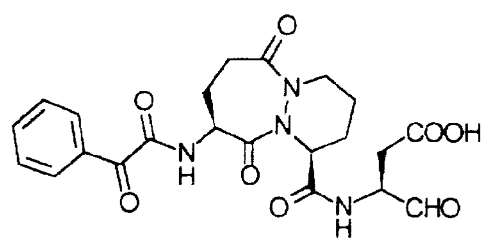
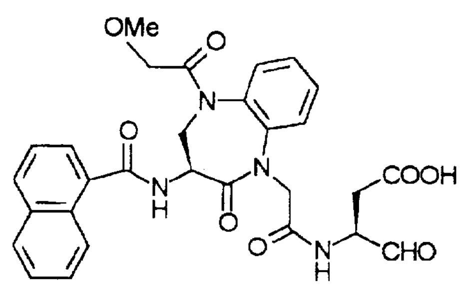
   CH2
\ /
 O   .
```

79. The compound according to claim 68, selected from the group consisting of:

2002  ; and

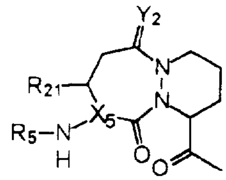
2201  .

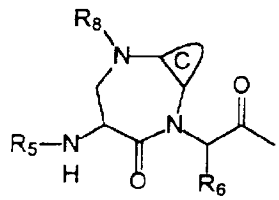
80. A compound represented by the formula:

$$(VI) \qquad R_1-\underset{\displaystyle H}{\underset{|}{N}}-R_2$$

wherein:

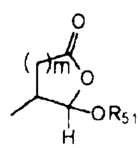
R_1 is:

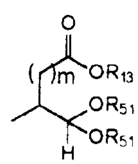
(e10)  , or

(w2)  ;

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl; the ring optionally being singly or multiply substituted by $-Q_1$;

R_2 is:

(a)  , or

(b)  ;

m is 1 or 2;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$-C(O)-N(R_{10})(R_{10})$

$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

X_5 is CH or N;

Y_2 is H_2 or O;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(H)-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$;
$-C(O)-CH_2N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9, $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group

consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

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 O
/ \
   CH2,
\ /
 O
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provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

81. The compound according to claim 80, wherein:

m is 1;

C is a ring chosen from the set consisting of benzo, pyrido, or thieno the ring optionally being singly or multiply substituted by halogen, $-NH_2$, $-NH-R_5$, $-NH-R_9$, $-OR_{10}$, or $-R_9$, wherein R_9 is a straight or branched C_{1-4} alkyl group, and R_{10} is H or a straight or branched C_{1-4} alkyl group;

R_6 is H;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted by $-Q_1$;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group

optionally substituted with $-Ar_3$, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
 O
/ \
   CH2,
\ /
 O
```

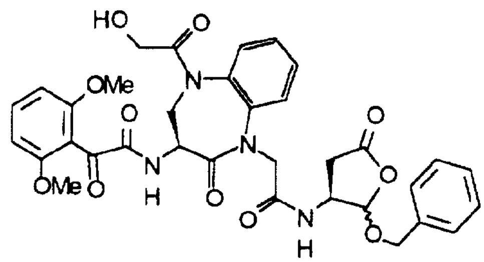
wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

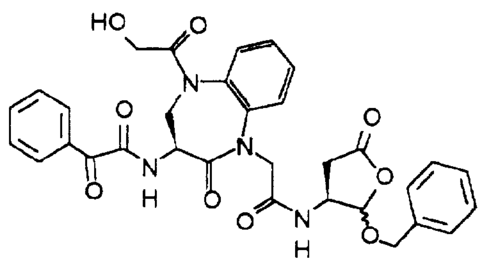
provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

82. The compound according to claim 81, wherein R_1 is (w2).

83. The compound according to claim 82,

selected from the group consisting of:

677  ; and

680  .

84. The compound according to claim 82, wherein R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$-C(O)-CH_2-OR_{10}$, and

$-C(O)-CH_2C(O)-R_9$.

85. The compound according to claim 84, wherein R_8 is $-C(O)-CH_2-OR_{10}$ and R_{10} is $-H$ or $-CH_3$.

86. The compound according to claim 81, wherein R_1 is (e10) and X_5 is CH.

87. The compound according to claim 81, wherein R_1 is (e10) and X_5 is N.

88. The compound according to any one of claims 80-87 wherein R_5 is $-C(O)-R_{10}$ or $-C(O)-C(O)-R_{10}$.

89. The compound according to claim 88, wherein R_{10} is Ar_3.

90. The compound according to claim 89, wherein:

R_5 is $-C(O)-R_{10}$ and R_{10} is Ar_3, wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

$-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group;

-F,

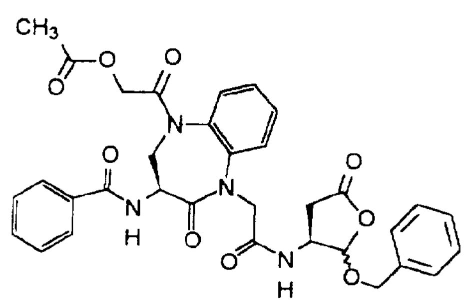
-Cl,

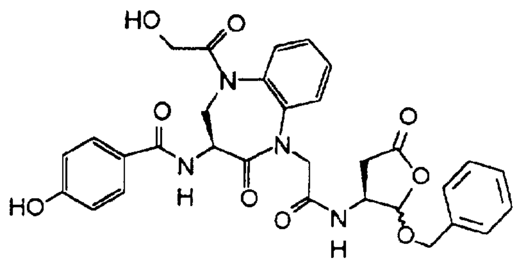
$-N(H)-R_5$, wherein $-R_5$ is -H or $-C(O)-R_{10}$, wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein Ar_3 is phenyl,

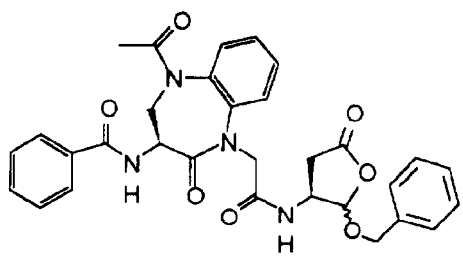
$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a $-C_{1-4}$ straight or branched alkyl group, or

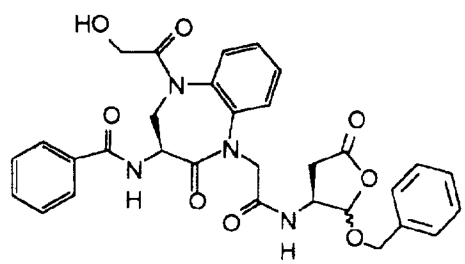
$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or branched alkyl group.

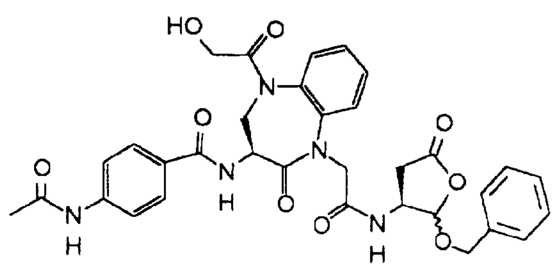
91. The compound according to claim 90, selected from the group consisting of:

682  ;

690b  ;

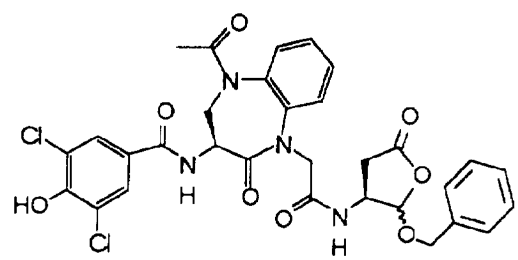
693  ;

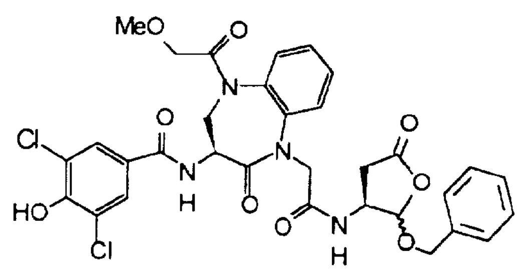
695a  ; and

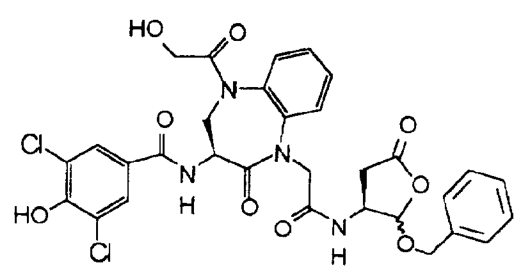
695b  .

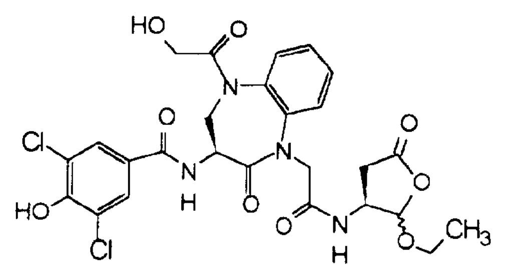
92. The compound according to claim 90, wherein Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by $-NH-R_5$, $-N(R_9)(R_{10})$, or $-O-R_5$.

93. The compound according to claim 92, selected from the group consisting of:

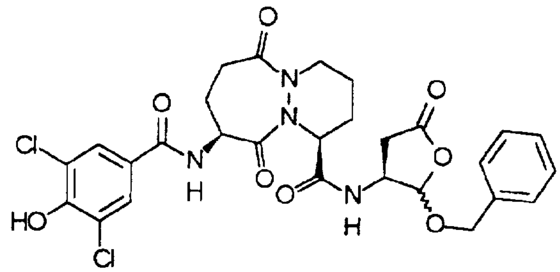
655  ;

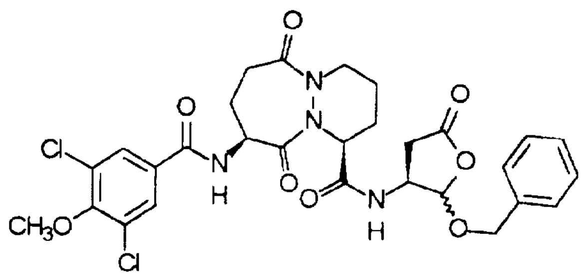
688a  ;

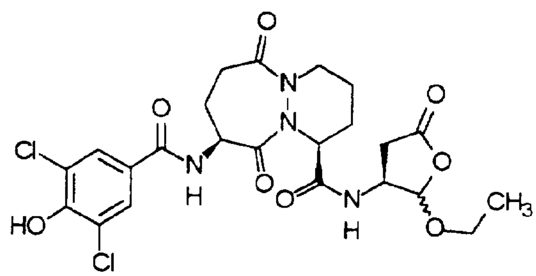
692a  ; and

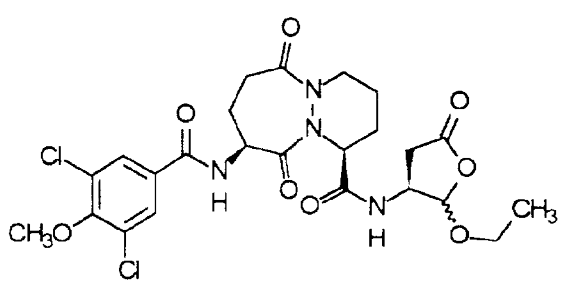
692b  .

94. The compound according to claim 92, selected from the group consisting of:

213k  ;

213m  ;

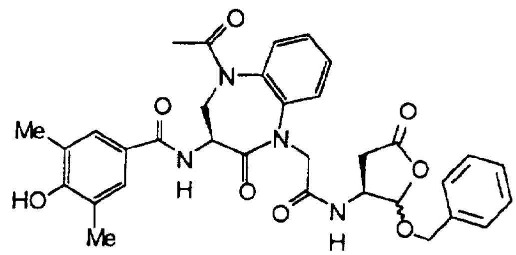
550k  ; and

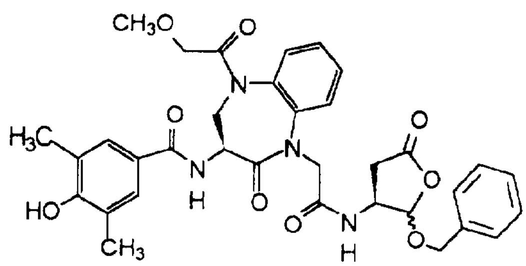
550m  .

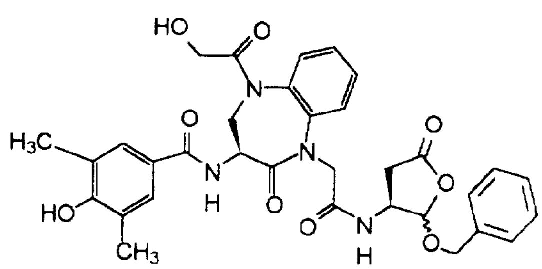
95. The compound according to claim 90, wherein Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by $-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group;

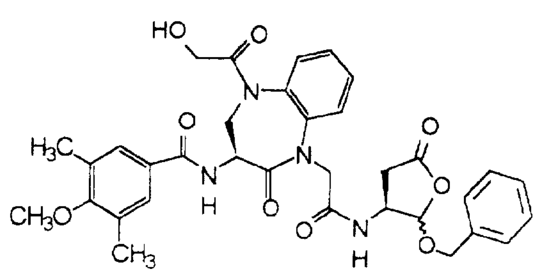
and at the 4-position by $-O-R_5$.

96. The compound according to claim 95, selected from the group consisting of:

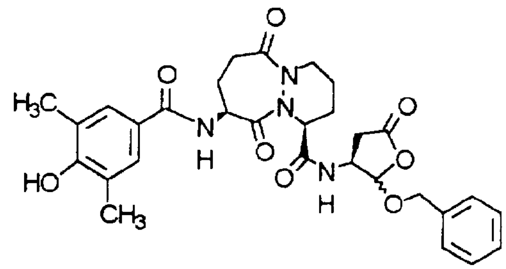
670  ;

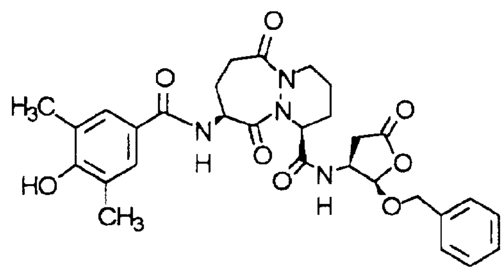
688b  ;

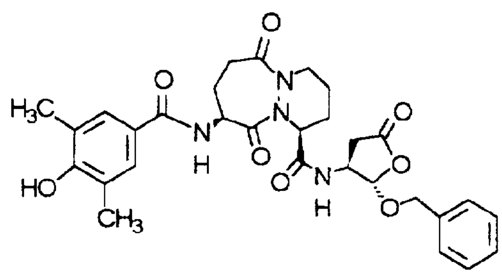
690a  ; and

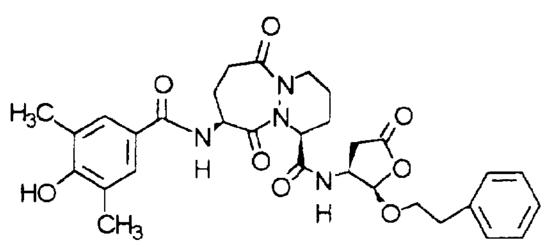
695c  .

97. The compound according to claim 95, selected from the group consisting of:

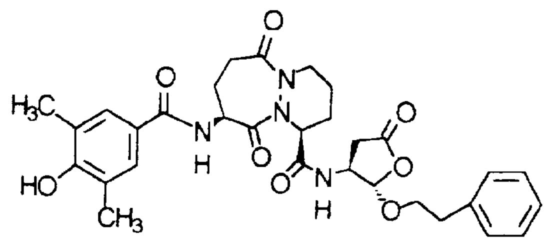
214w-1  ;

214w-2  ;

214w-3  ;

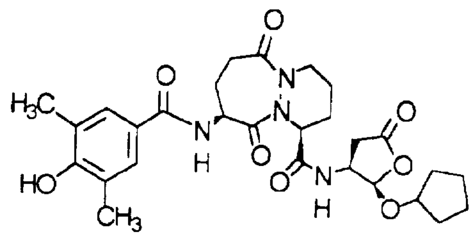
214w-4  ;

214w-5



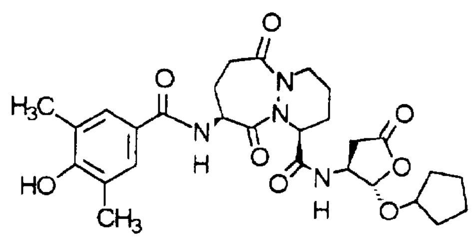
;

214w-6



; and

214w-7



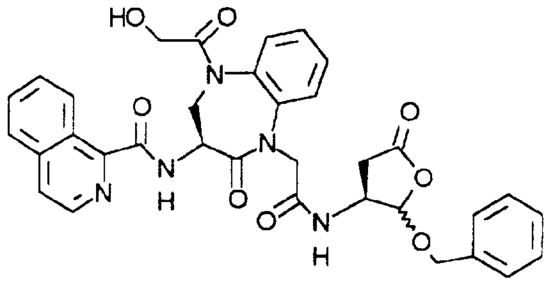
.

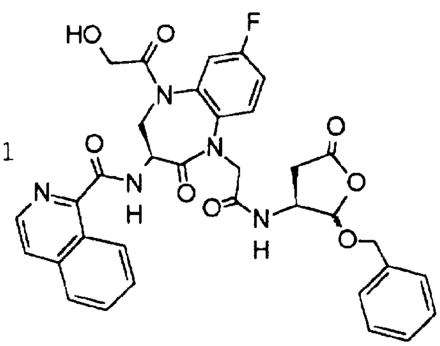
98. The compound according to claim 89, wherein:

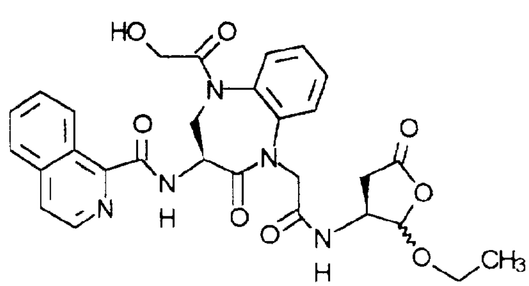
R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

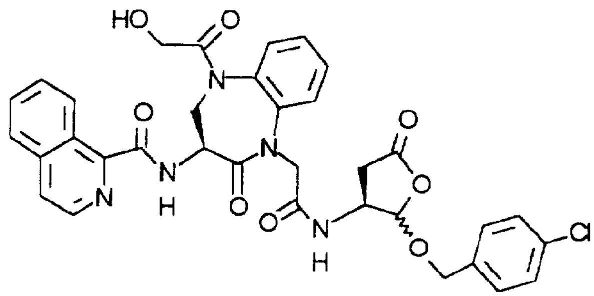
99. The compound according to claim 98, wherein the Ar_3 cyclic group is isoquinolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

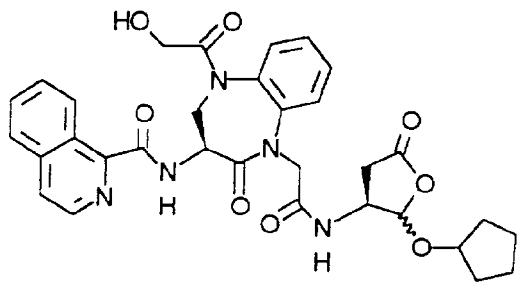
100. The compound according to claim 99 selected from the group consisting of:

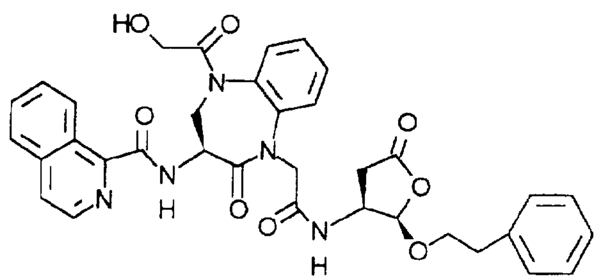
696a  ;

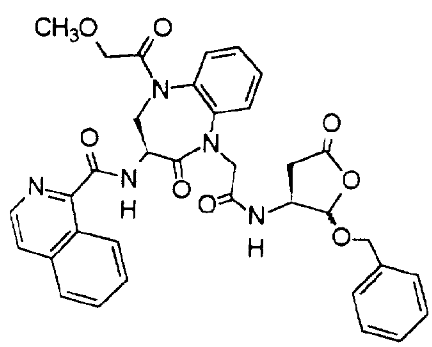
696a-1  ;

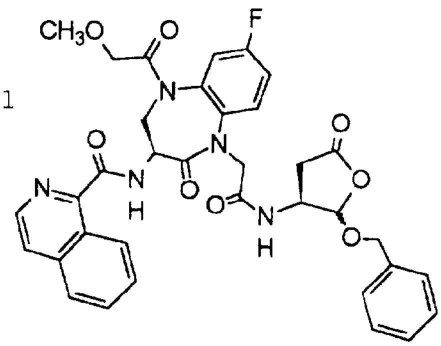
696b  ;

696c  ;

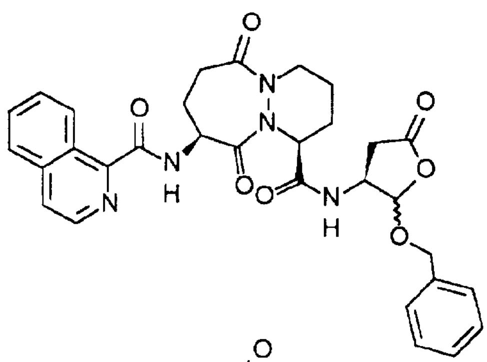
696d  ;

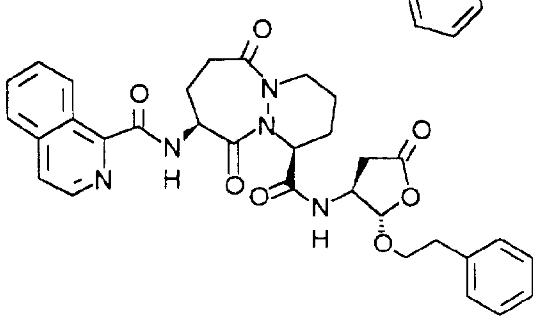
696e  ;

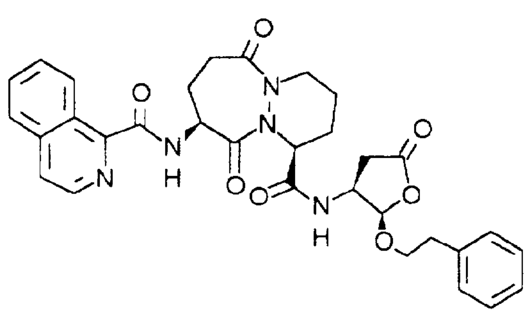
699a  ; and

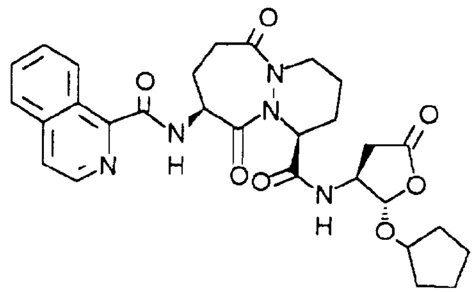
699a-1  .

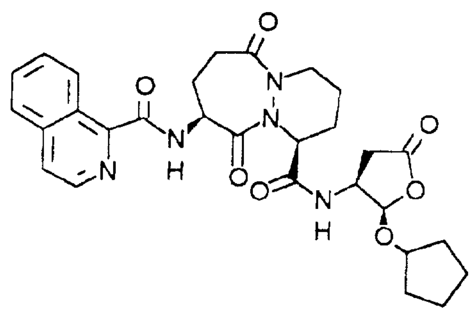
101. The compound according to claim 99, selected from the group consisting of:

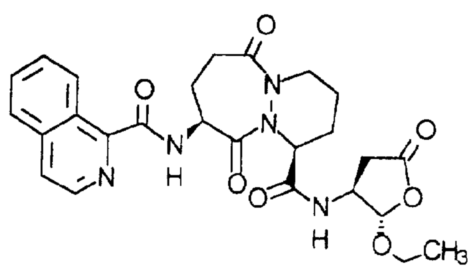
213y  ;

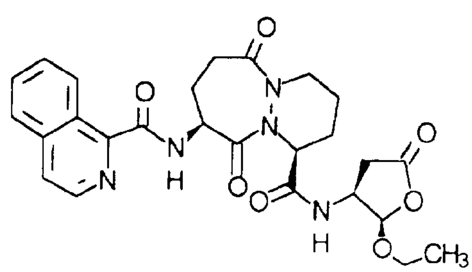
412a  ;

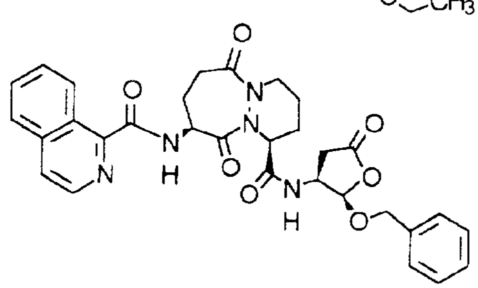
412b  ;

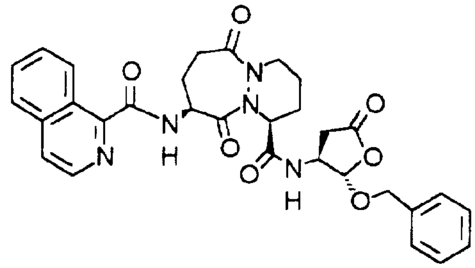
412c  ;

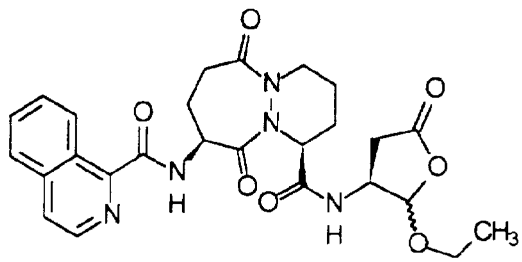
412d  ;

412e  ;

412f  ;

412g  ;

412h  ; and

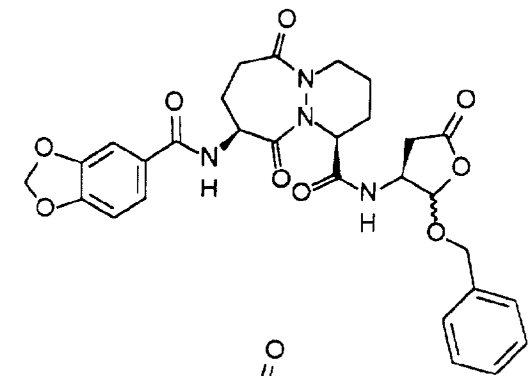
550q  .

102. The compound according to claim 89, wherein R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is phenyl, substituted by

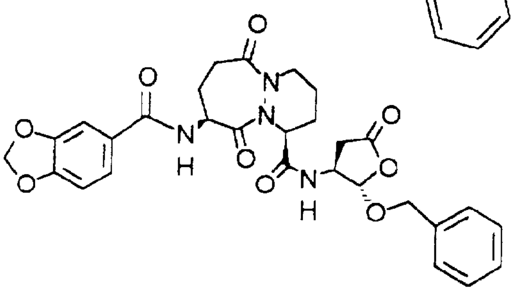
```
  O
 / \
    CH2
 \ /
  O   .
```

103. The compound according to claim 102, selected from the group consisting of:

213n

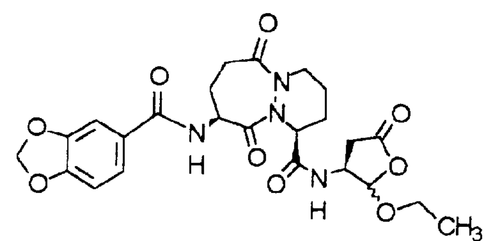


415a



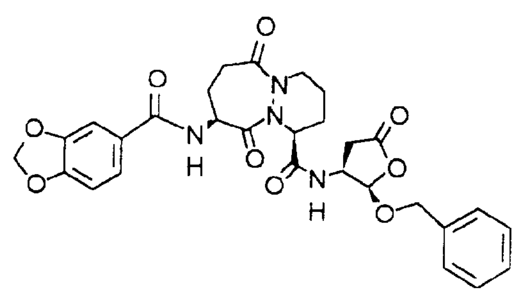
;

415b



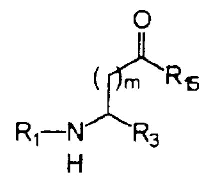
; and

415c



.

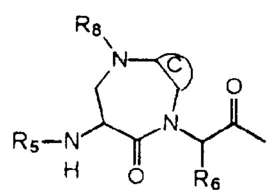
104. A compound represented by the formula:

(VII) 

wherein:

m is 1 or 2;

R_1 is selected from the group consisting of the following formulae:

(w2)  ;

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being singly or multiply substituted by $-Q_1$,;

R_3 is selected from the group consisting of:

$-CN$,

$-C(O)-H$,

$-C(O)-CH_2-T_1-R_{11}$,

$-C(O)-CH_2-F$,

$-C=N-O-R_9$, and

$-CO-Ar_2$;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,
$-C(O)-N(R_{10})(R_{10})$
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched

alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

$-Ar_4$,

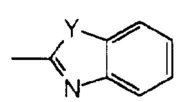
$-(CH_2)_{1-3}-Ar_4$,

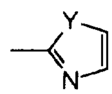
-H, and

$-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN,

=O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

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  O
 / \
    CH2;
 \ /
  O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

105. The compound according to claim 104, wherein:

m is 1;

C is a ring chosen from the set consisting of benzo, pyrido, and thieno, the ring optionally being singly or multiply substituted by halogen, $-NH_2$, $-NH-R_5$, or $-NH-R_9$, $-OR_{10}$, or $-R_9$, wherein R_9 is a straight or branched C_{1-4} alkyl group, and R_{10} is H or a straight or branched C_{1-4} alkyl group;

T_1 is O or S;

R_6 is H;

R_{11} is selected from the group consisting of $-Ar_4$, $-(CH_2)_{1-3}-Ar_4$, and $-C(O)-Ar_4$;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
 O
/ \
   CH2,
\ /
 O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

106. The compound according to claim 105, wherein R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-CH_2-OR_{10}$, and
$-C(O)-CH_2C(O)-R_9$.

107. The compound according to claim 106, wherein R_8 is $-C(O)-CH_2-OR_{10}$ and R_{10} is -H or $-CH_3$.

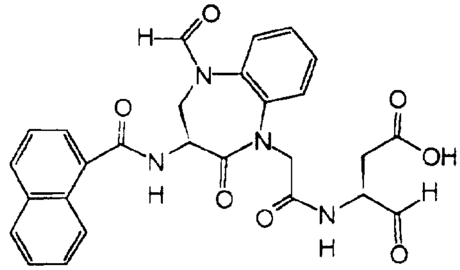
108. The compound according to claim 105, wherein R_3 is $-C(O)-Ar_2$,

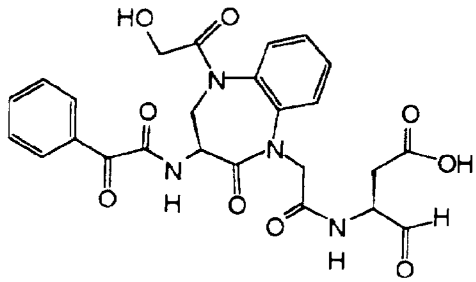
109. The compound according to claim 105, wherein R_3 is $-C(O)CH_2-T_1-R_{11}$;

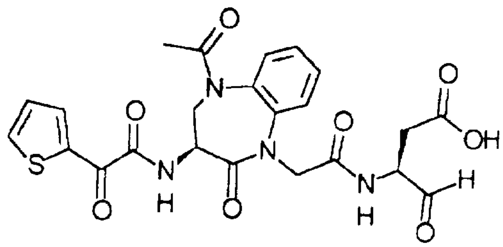
110. The compound according to claim 105, wherein R_3 is -C(O)-H.

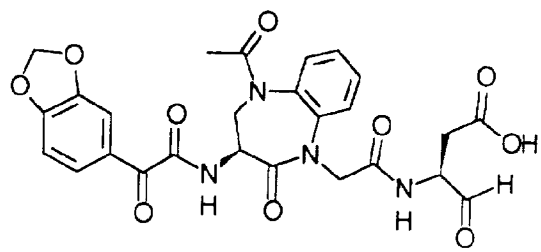
111. The compound according to claim 110, wherein R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-CH_2-OR_{10}$, and
$-C(O)-CH_2C(O)-R_9$.

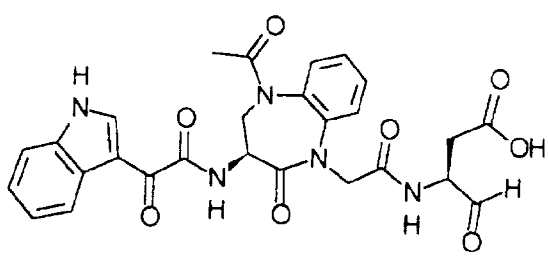
112. The compound according to claim 111, selected from the group consisting of:

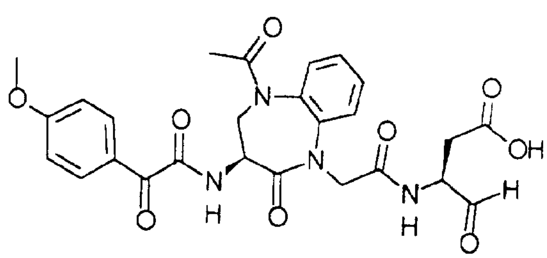
653  ;

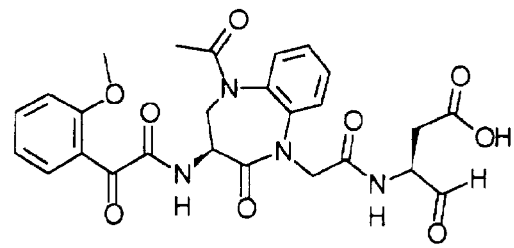
681  ;

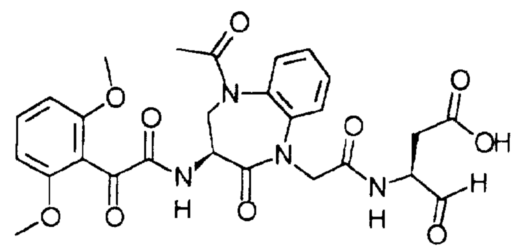
701  ;

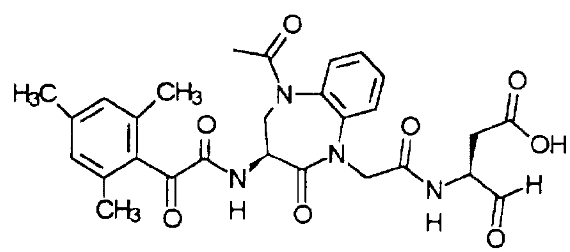
702  ;

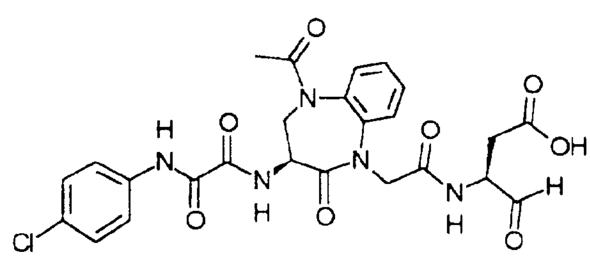
703  ;

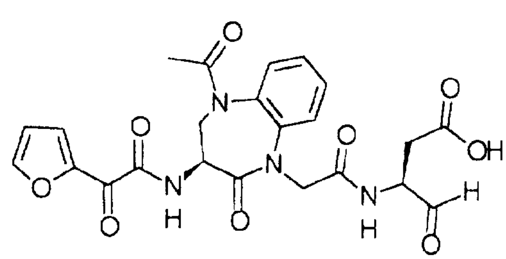
704  ;

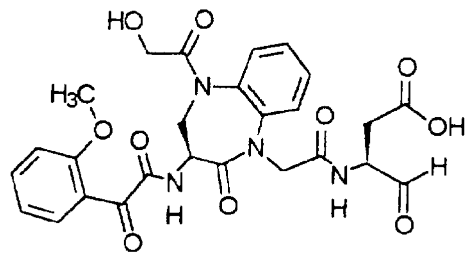
705  ;

706  ;

709  ;

710  ;

711  ; and

921  .

113. The compound according to claim 111, wherein R_8 is $-C(O)-CH_2-OR_{10}$ and R_{10} is -H or $-CH_3$.

114. The compound according to claim 68, wherein:

m is 1;

T_1 is O or S;

R_{21} is -H or $-CH_3$;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl and said cyclic group being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl

and said cyclic group being singly or multiply substituted by
$-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
    O
   / \
      CH2,
   \ /
    O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

115. The compound according to claim 114, wherein R_3 is $-C(O)-Ar_2$,

116. The compound according to claim 114, wherein R_3 is $-C(O)CH_2-T_1-R_{11}$;

117. The compound according to claim 114, wherein R_3 is $-C(O)-H$.

118. The compound according to any one of claims 104-117, wherein R_5 is $-C(O)-R_{10}$ or $-C(O)C(O)-R_{10}$.

119. The compound according to claim 118, wherein R_{10} is Ar_3.

120. The compound according to claim 119, wherein:

R_5 is $-C(O)-R_{10}$ and R_{10} is Ar_3, wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

$-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group;

-F,

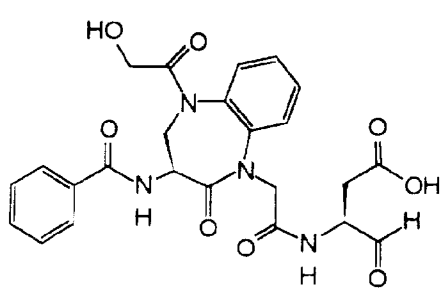
-Cl,

$-N(H)-R_5$, wherein $-R_5$ is -H or $-C(O)-R_{10}$, wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein Ar_3 is phenyl,

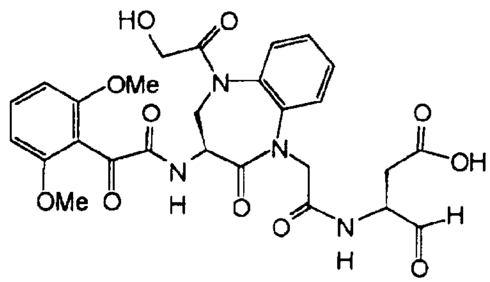
$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a $-C_{1-4}$ straight or branched alkyl group, or

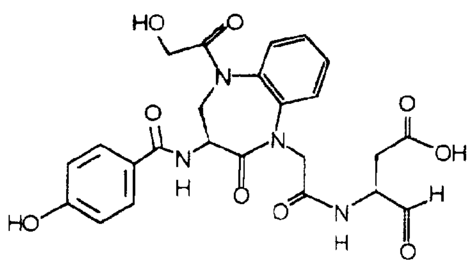
$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or branched alkyl group.

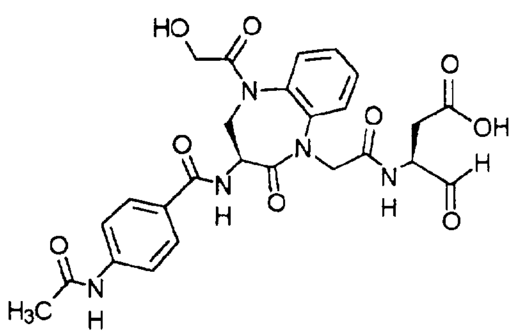
121. The compound according to claim 120, selected from the group consisting of:

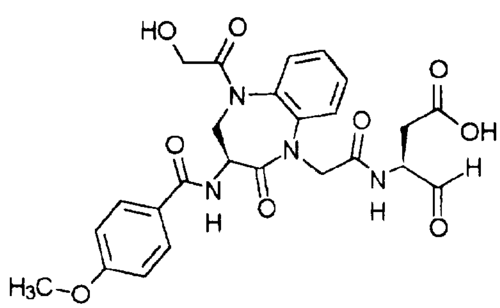
668 

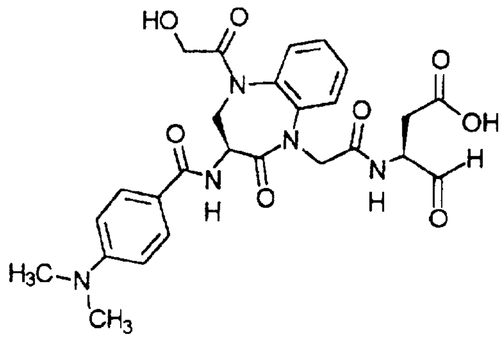
;

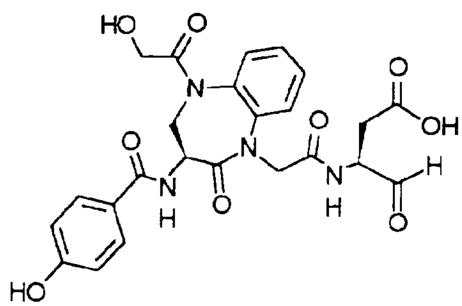
678  ;

691b  ;

911  ;

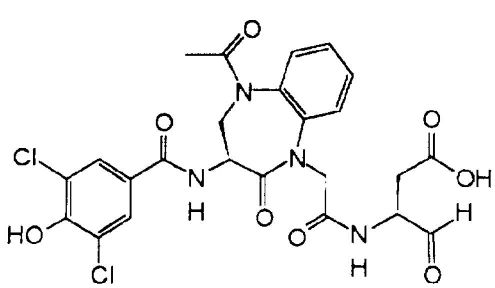
912  ;

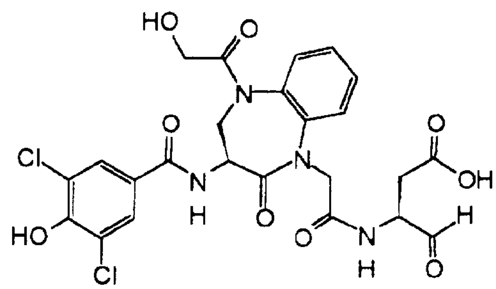
913  ; and

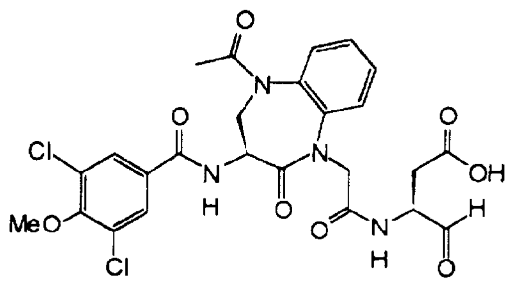
916  .

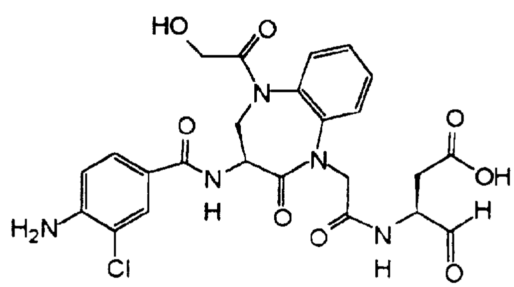
122. The compound according to claim 120, wherein Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by $-NH-R_5$, $-N(R_9)(R_{10})$, or $-O-R_5$.

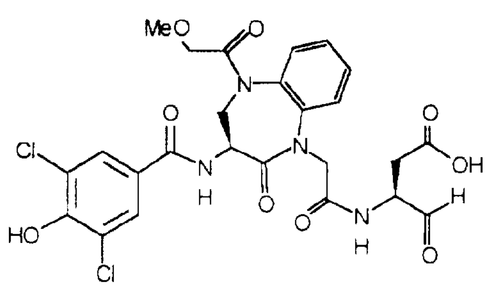
123. The compound according to claim 122, selected from the group consisting of:

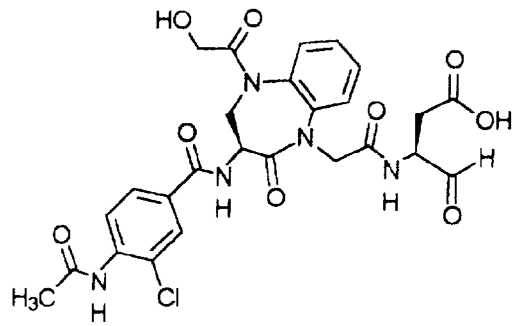
656  ;

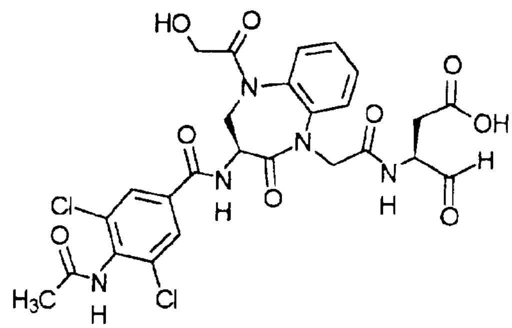
662  ;

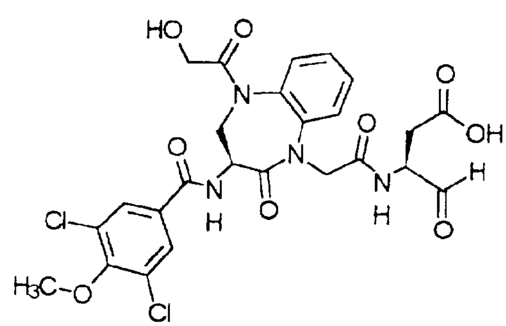
669  ;

686  ;

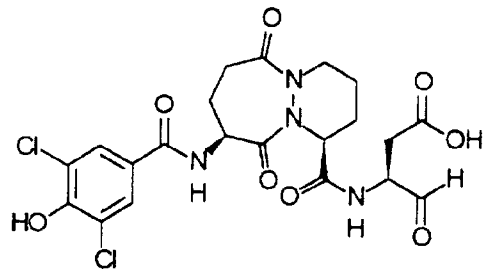
689a  ;

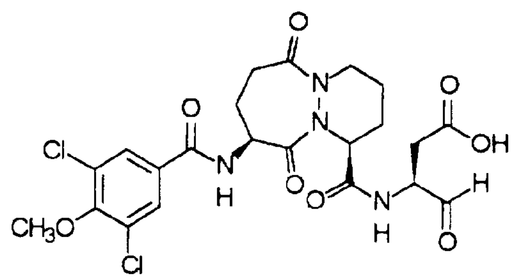
914  ;

915  ; and

918  .

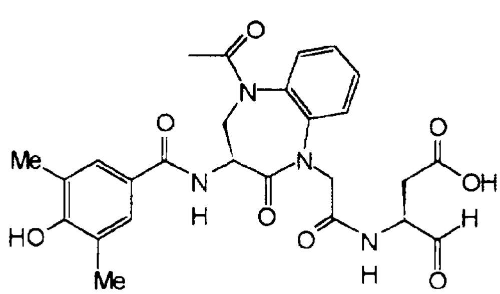
124. The compound according to claim 122, selected from the group consisting of:

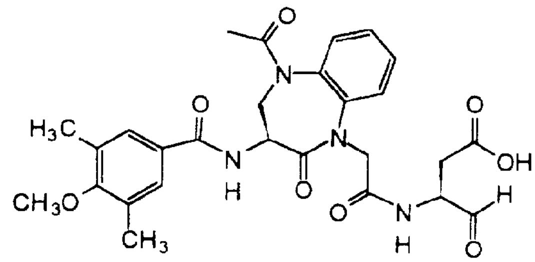
214k  ; and

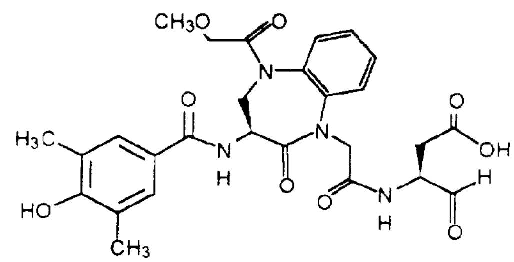
214m  .

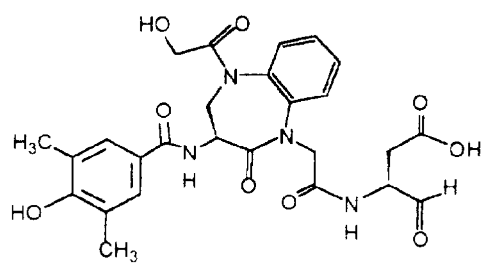
125. The compound according to claim 120, wherein Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by $-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group; and at the 4-position by $-O-R_5$.

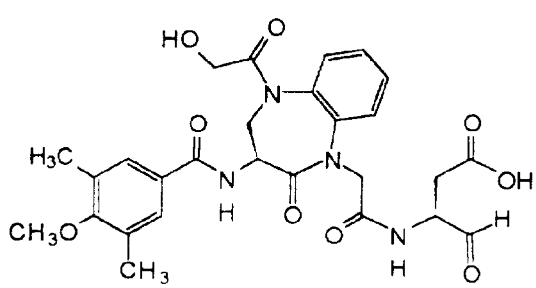
126. The compound according to claim 125, selected from the group consisting of:

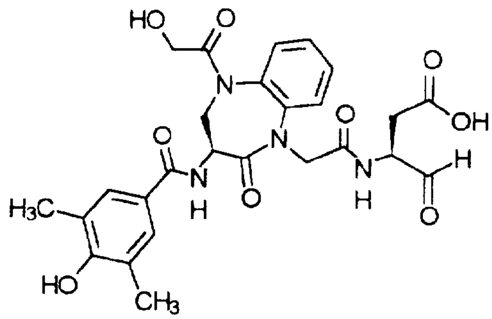
671  ;

684  ;

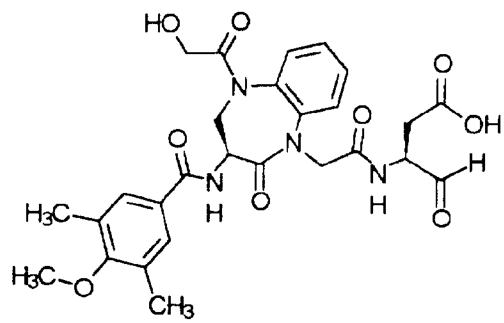
689b  ;

691a  ;

694  ;

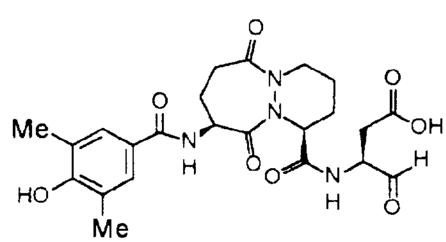
917 

; and

922 

.

127. The compound according to claim 125, wherein the compound is:

214w 

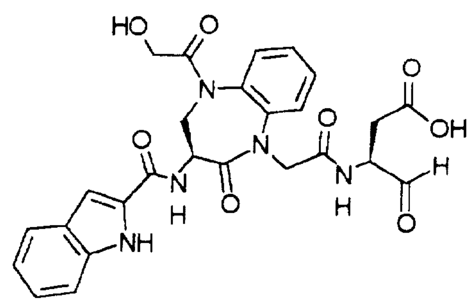
.

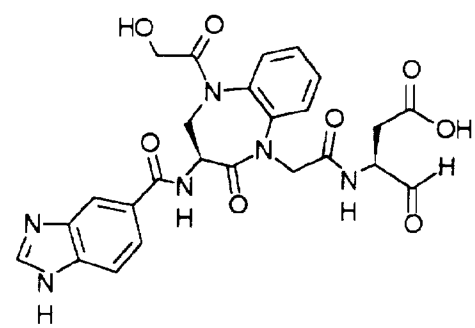
128. The compound according to claim 119, wherein:

R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted

by $-Q_1$.

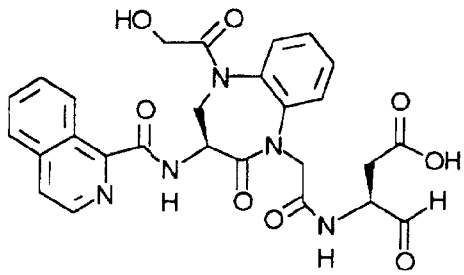
129. The compound according to claim 128, selected from the group consisting of:

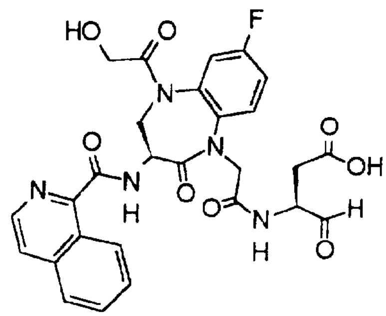
919  ; and

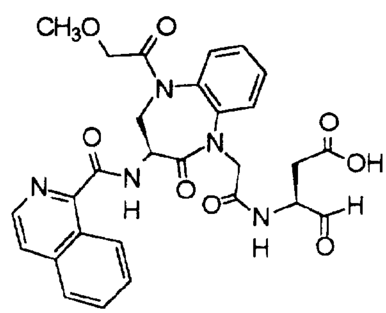
920  .

130. The compound according to claim 128, wherein the Ar_3 cyclic group is isoquinolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

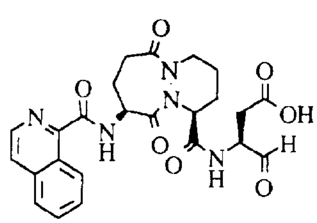
131. The compound according to claim 130, wherein the compound is:

696  ;

696-1  ; and

699  .

132. The compound according to claim 130, wherein the compound is:

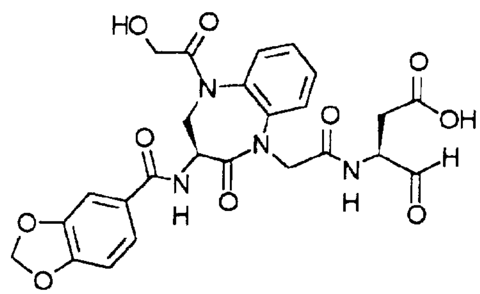
412  .

133. The compound according to claim 119, wherein R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3

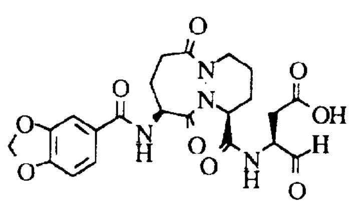
cyclic group is phenyl, substituted by

```
      O
     / \
        CH2
     \ /
      O    .
```

134. The compound according to claim 133, wherein the compound is:

910  .

135. The compound according to claim 133, wherein the compound is:

415  .

136. A pharmaceutical composition, comprising a compound according to any one of claims 1-41 and 57-135 in an amount effective for decreasing IGIF production and a pharmaceutically acceptable carrier.

137. A pharmaceutical composition comprising a compound according to any one of claims 1-41 and 57-135 in an amount effective for decreasing IFN-γ

production and a pharmaceutically acceptable carrier.

138. A method for treating or preventing a disease selected from an IGIF mediated disease, an IFN-γ mediated disease, an inflammatory disease, an autoimmune disease, an infectious disease, a proliferative disease, a neurodegenerative disease, a necrotic disease, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative collitis, cerebral ischemia, myocardial ischemia, adult respiratory distress syndrome, infectious hepatitis, sepsis, septic shock, Shigellosis, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, acute dermatomyositis, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome comprising the step of administering to said patient a pharmaceutical composition according to claims 136 or 137.

139. The method according to claim 138, wherein the disease is selected from an inflammatory disease, an autoimmune disease, an infectious disease, rheumatoid arthritis, ulcerative collitis, Crohn's disease, hepatitis, adult respiratory distress syndrome, glomerulonephritis, insulin-dependent

diabetes mellitus (Type I), juvenile diabetes, psoriasis, graft vs. host disease, and hepatitis.

140. A process for preparing an N-acylamino compound, comprising the steps of:

a) mixing a carboxylic acid with an N-alloc-protected amine in the presence of an inert solvent, triphenylphoshine, a nucleophilic scavenger, and tetrakis-triphenyl phosphine palladium(0) at ambient temperature under an inert atmosphere; and

b) adding to the step a) mixture, HOBT and EDC; and optionally comprising the further step of:

c) hydrolyzing the step b) mixture in the presence of a solution comprising an acid and H_2O, wherein the step b) mixture is optionally concentrated.

141. The process according to claim 140, wherein the inert solvent is CH_2Cl_2, DMF, or a mixture of CH_2Cl_2 and DMF.

142. The process according to claim 140, wherein the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine or dimethyl barbituric acid.

143. The process according to claim 142, wherein the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

144. The process according to claim 142, wherein the inert solvent is CH_2Cl_2, DMF, or a mixture

of CH_2Cl_2 and DMF.

145. The process according to claim 144, wherein the nucleophilic scavenger is dimethyl barbituric acid.

146. The process according to claim 145, wherein the solution comprises trifluoroacetic acid in about 1-90% by weight.

147. The process according to claim 146, wherein the solution comprises trifluoroacetic acid in about 20-50% by weight.

148. The process according to claim 145, wherein the solution comprises hydrochloric acid in about 0.1-30% by weight.

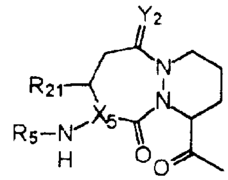
149. The process according to claim 148, wherein the solution comprises hydrochloric acid in about 5-15% by weight.

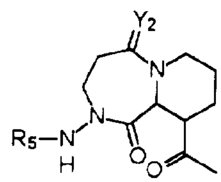
150. The process according to any one of claims 140-149, wherein the N-acylamino compound is represented by formula (VIII):

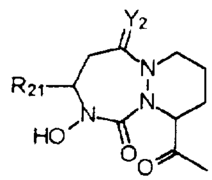
$$\text{(VIII)} \qquad R_1\text{-}\underset{\displaystyle H}{\underset{|}{N}}\text{-}R_2$$

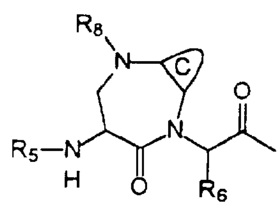
wherein:

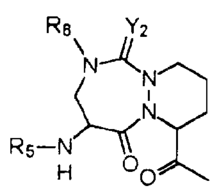
R_1 is selected from the group consisting of the following formulae:

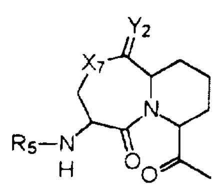
(e10)  ;

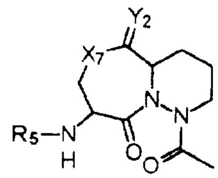
(e11)  ;

(e12)  ;

(w2)  ;

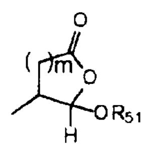
(y1)  ;

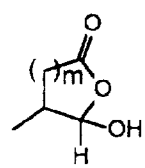
(y2)  ;

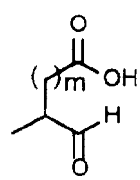
(z)  ; and

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being singly or multiply substituted by halogen, $-NH_2$, or $-NH-R_9$,;

R_2 is:

(a)  ,

(b)  , or

(c)  ;

m is 1 or 2;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,
$-C(O)-N(R_{10})(R_{10})$
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

X_5 is CH or N;

Y_2 is H_2 or O;

X_7 is $-N(R_8)-$ or $-O-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(H)-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$;
$-C(O)-CH_2N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
$-H$, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9, $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally

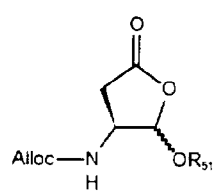
comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

```
 O
/ \
   CH2,
\ /
 O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$;

151. The process according to any one of claims 140 -149 wherein the N-alloc protected amine is:

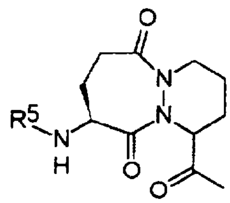


, wherein:

R_{51} is independently selected from the group consisting of R_9, $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

152. The process according to any one of claims 140-149, wherein R_1 is:

(A-e10)



153. The process according to any one of claims 140-149, wherein R_1 is:

(A-w2)

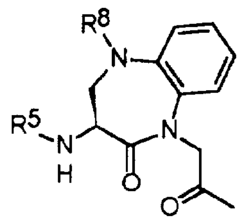


FIG. 1A

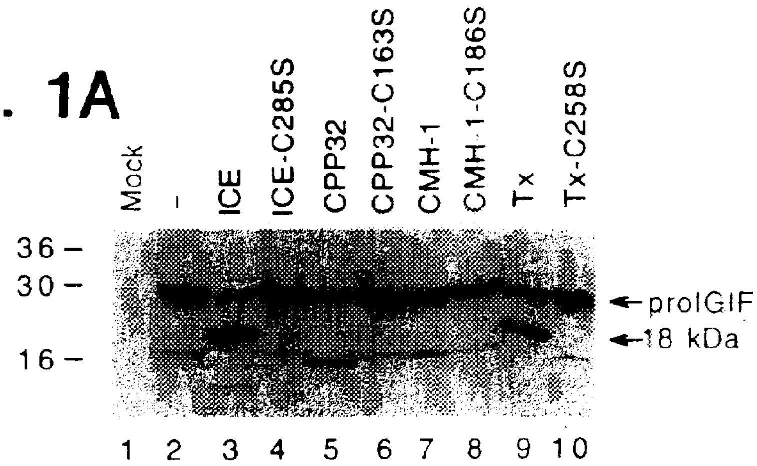


FIG. 1B

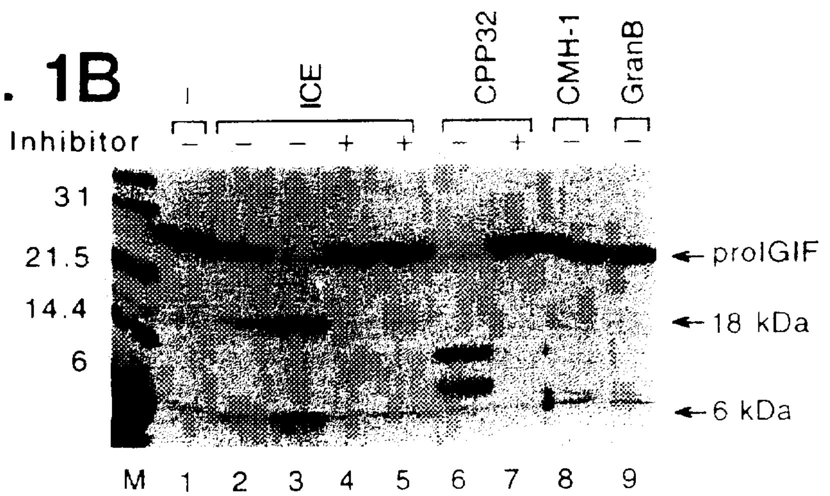


FIG. 1C

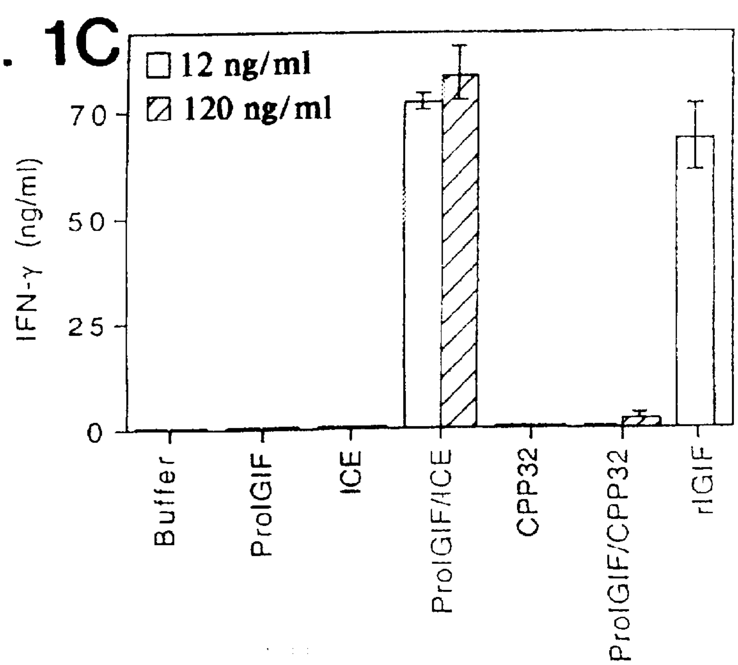
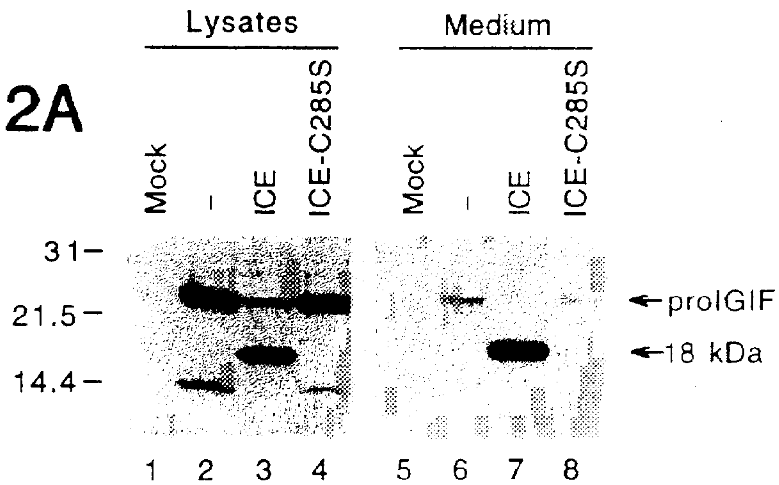


FIG. 2A


Lysates
Medium
Mock
-
ICE
ICE-C285S
Mock
-
ICE
ICE-C285S
31
21.5
14.4
proIGIF
18 kDa
1 2 3 4 5 6 7 8

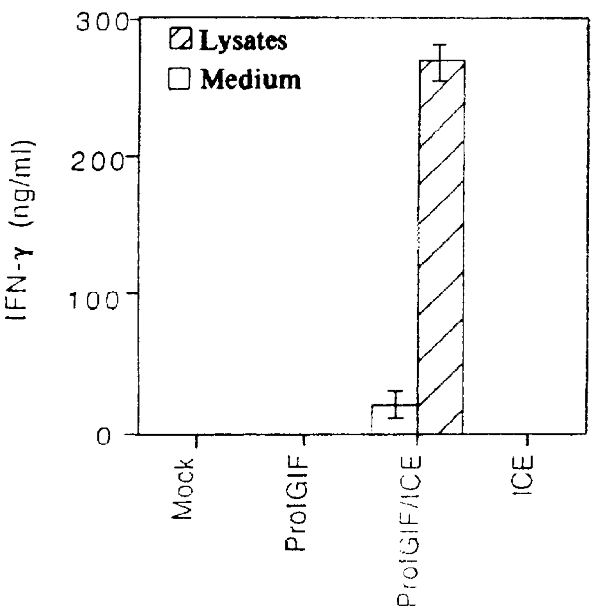

Lysates
Medium
IFN-γ (ng/ml)
300
200
100
0
Mock
ProIGIF
ProIGIF/ICE
ICE

FIG. 2B

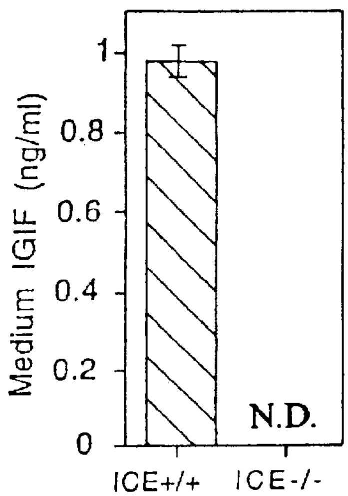


FIG. 3A

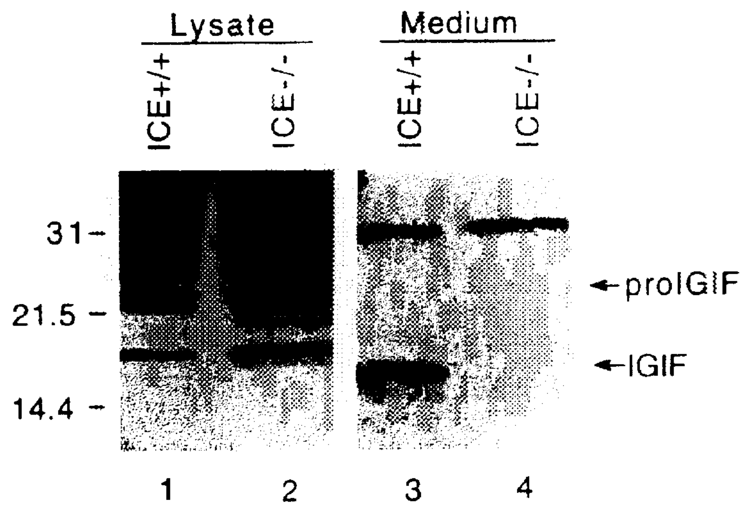


FIG. 3B

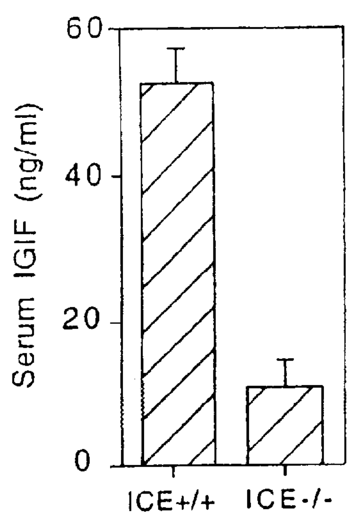


FIG. 3C

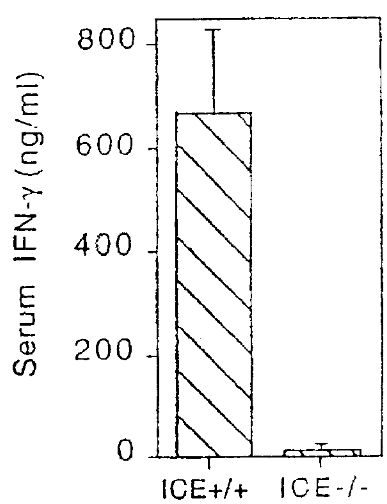


FIG. 3D

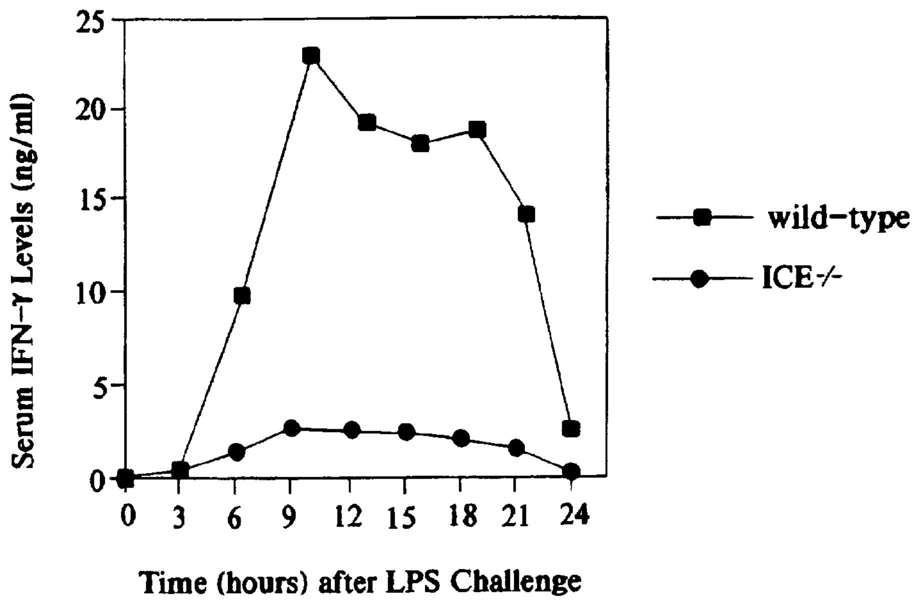

25
20
15
10
5
0
Serum IFN-γ Levels (ng/ml)
0 3 6 9 12 15 18 21 24
Time (hours) after LPS Challenge
wild-type
ICE-/-

FIG. 4

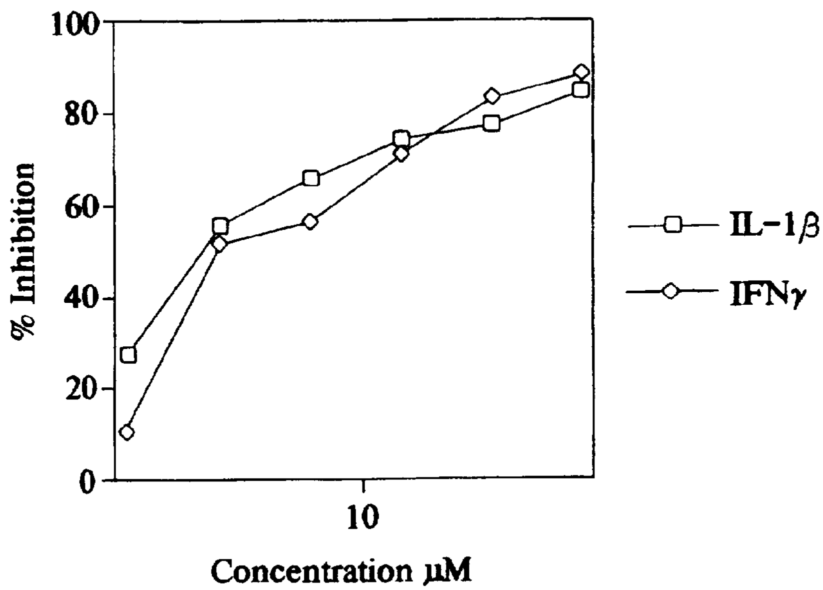

100
80
60
40
20
0
% Inhibition
10
Concentration μM
IL-1β
IFNγ

FIG. 5

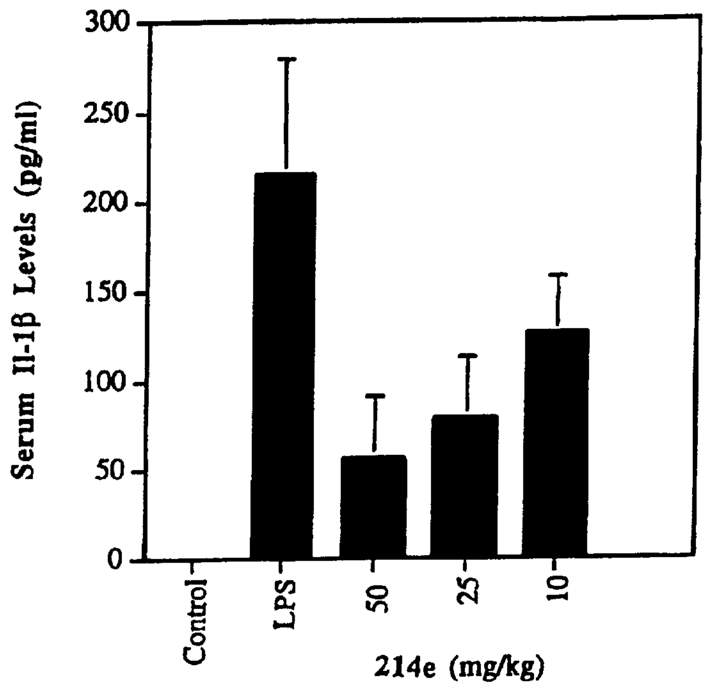

300
250
200
150
100
50
0
Serum Il-1β Levels (pg/ml)
Control
LPS
50
25
10
214e (mg/kg)

FIG. 6

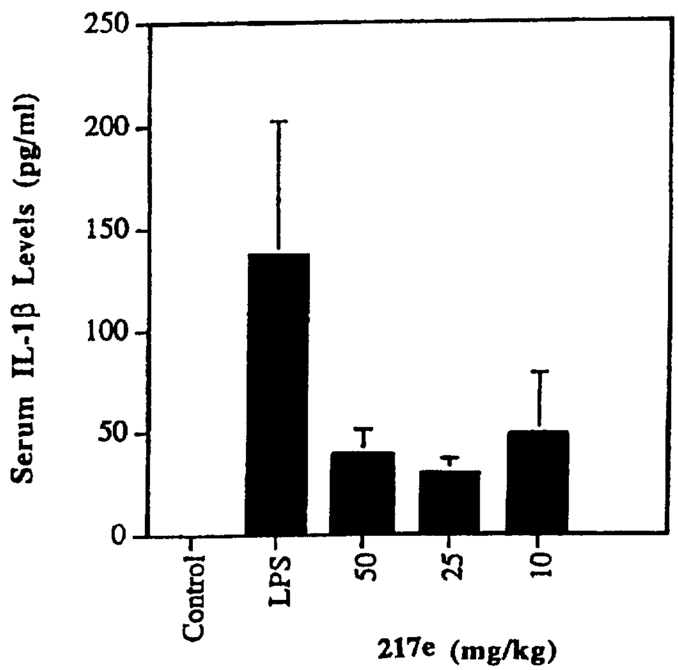

250
200
150
100
50
0
Serum IL-1β Levels (pg/ml)
Control
LPS
50
25
10
217e (mg/kg)

FIG. 7

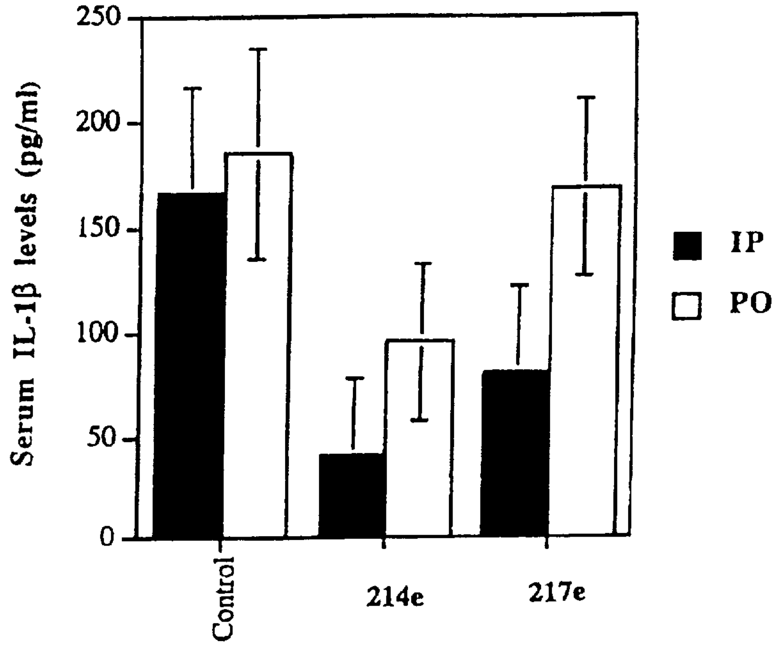

250
200
150
100
50
0
Serum IL-1β levels (pg/ml)
Control
214e
217e
IP
PO

FIG. 8

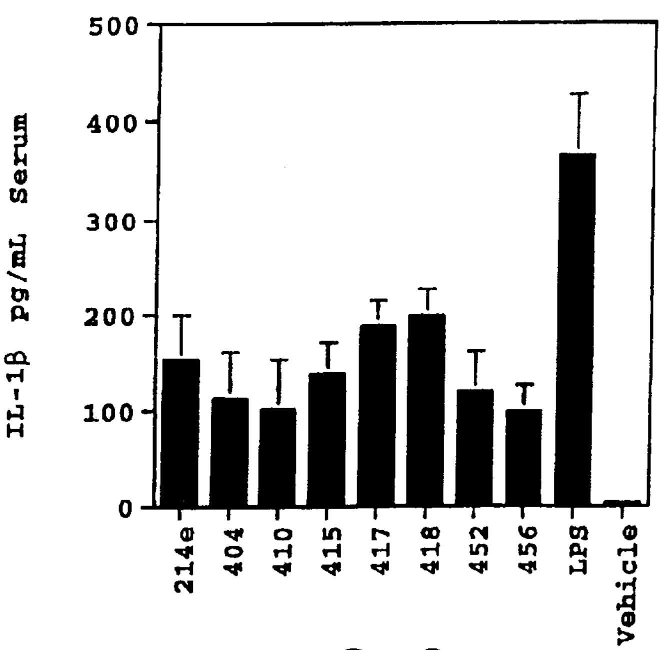

500
400
300
200
100
0
IL-1β pg/mL Serum
214e
404
410
415
417
418
452
456
LPS
Vehicle

FIG. 9

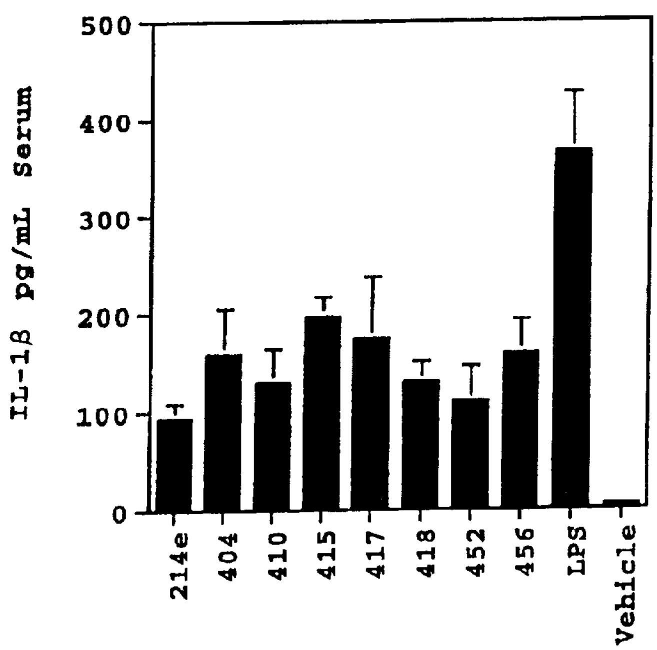

IL-1β pg/mL Serum
500
400
300
200
100
0
214e
404
410
415
417
418
452
456
LPS
Vehicle

FIG. 10

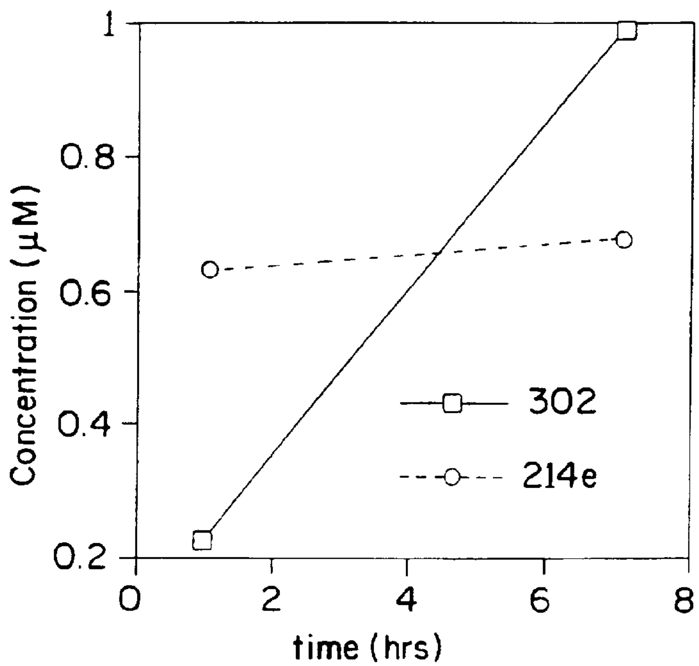


FIG. 11A

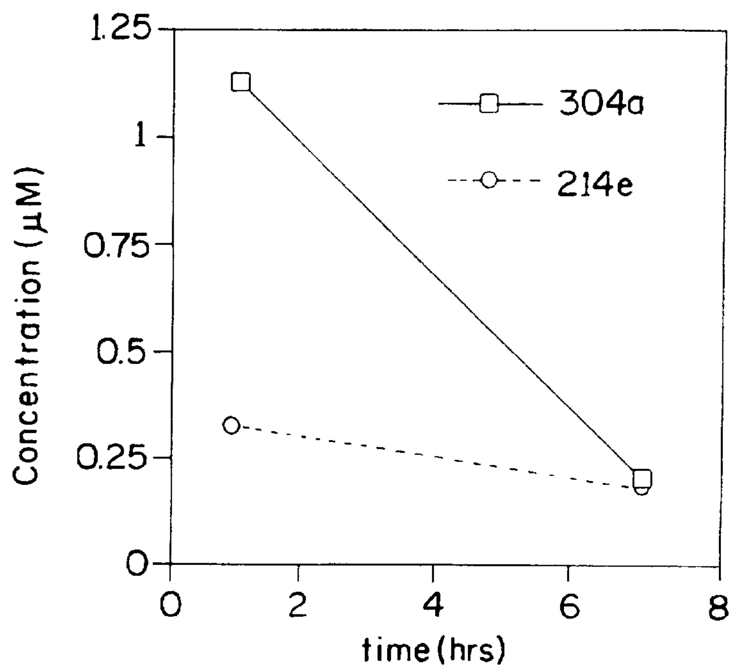


FIG. 11B

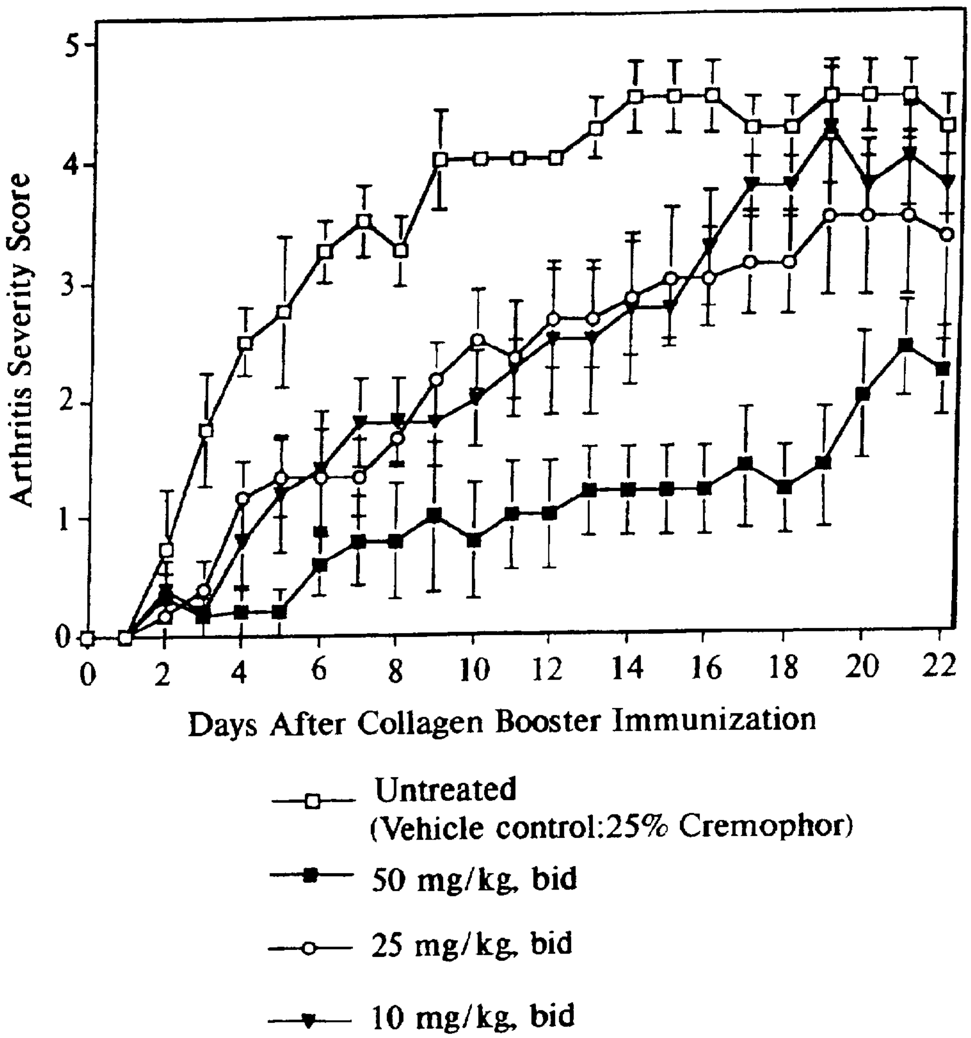

Arthritis Severity Score
0
1
2
3
4
5
0 2 4 6 8 10 12 14 16 18 20 22
Days After Collagen Booster Immunization
Untreated
(Vehicle control:25% Cremophor)
50 mg/kg, bid
25 mg/kg, bid
10 mg/kg, bid

FIG. 12

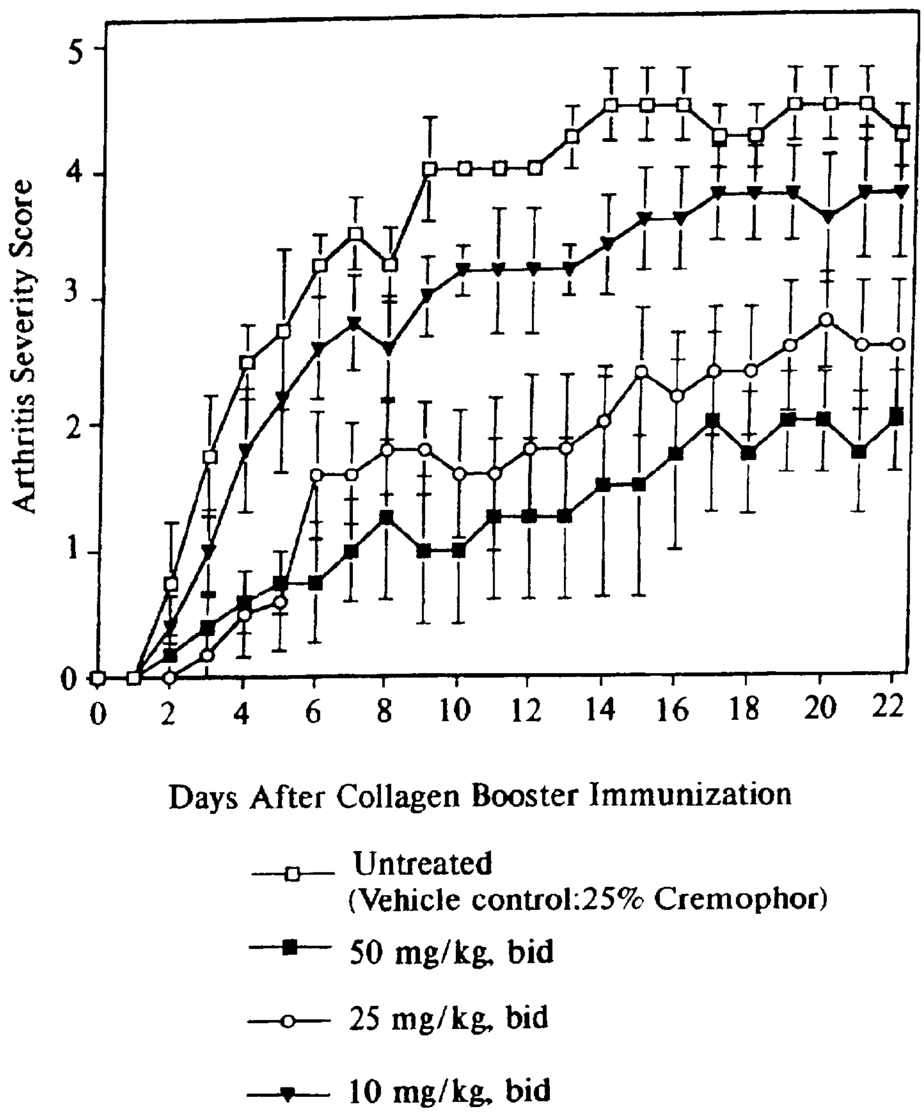

5
4
3
2
1
0
Arthritis Severity Score
0
2
4
6
8
10
12
14
16
18
20
22
Days After Collagen Booster Immunization
Untreated
(Vehicle control:25% Cremophor)
50 mg/kg, bid
25 mg/kg, bid
10 mg/kg, bid

FIG. 13

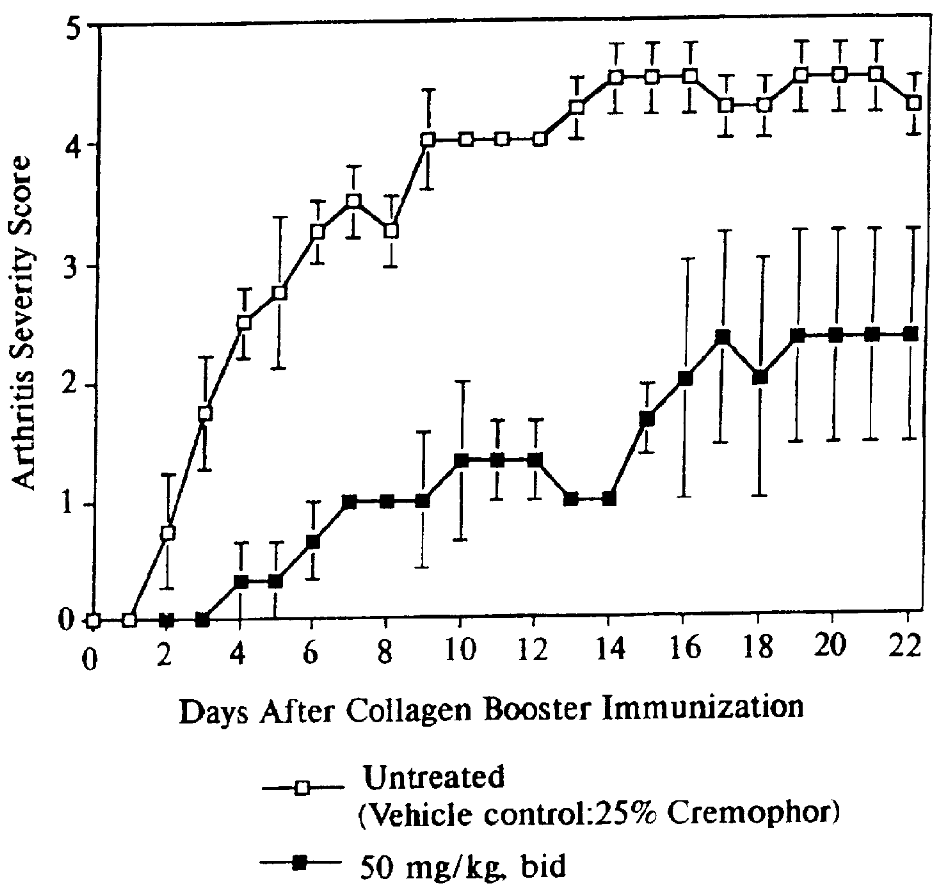

Arthritis Severity Score
0
1
2
3
4
5
0 2 4 6 8 10 12 14 16 18 20 22
Days After Collagen Booster Immunization
Untreated
(Vehicle control:25% Cremophor)
50 mg/kg, bid

FIG. 14

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08/761,483	6 December 1996 (06.12.96)	US

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(54) Title: INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME

(57) Abstract

The present invention relates to novel classes of compounds which are inhibitors of interleukin-1β converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against IL-1-, apoptosis-, IGIF-, and IFN-γ- mediated diseases, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, and necrotic diseases. This invention also relates to methods for inhibiting ICE activity, for treating interleukin-1-, apoptosis-, IGIF- and IFN-γ-mediated diseases and decreasing IGIF and IFN-γ production using the compounds and compositions of this invention. This invention also relates to methods for preparing N-acylamino compounds.

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US	United States of America
UZ	Uzbekistan
VN	Viet Nam

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/20843

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/023 C07D487/04 C07D498/04 A61K38/04 A61K31/55
//(C07D487/04,243:00,237:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 135 349 A (TAKEDA CHEMICAL INDUSTRIES LTD) 27 March 1985 see claims 1-4,41-43; examples 24,25 --- -/--	1,42-56, 136-139

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
28 August 1997	04.09.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 33751 A (SANOFI WINTHROP INC) 14 December 1995	4-8, 16-38, 40-57, 59-62, 64-81, 86-90, 92,94, 95, 97-99, 101-103, 114-120, 122
X	see the whole document	124,125, 127,128, 130,132, 133, 135-139
P,X	WO 95 35308 A (VERTEX PHARMA) 28 December 1995 see the whole document	1-8, 14-139
A	EP 0 644 198 A (STERLING WINTHROP INC) 22 March 1995 see the whole document	1-8, 14-139
A	WO 95 26958 A (SANOFI WINTHROP INC) 12 October 1995 cited in the application see the whole document	1-8, 14-139
A	EP 0 618 223 A (SANDOZ LTD ;SANDOZ AG (DE); SANDOZ AG (AT)) 5 October 1994 see claims 1-10; example 92	1-8, 14-139
T	JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, no. 13, 20 June 1997, WASHINGTON US, pages 1941-1946, XP002039102 DOLLE E.A.: "Pyridazinodiazepines as a high-affinity, P2-P3 peptidomimetic class of ICE inhibitor" see the whole document	1-8, 14-139

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 55,56,138,139
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 55,56,138,139
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See next page

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
Subject 1: Claims 1-13,14,15,39,58,63,82-85,91,93,96,100,104-113,121,123,126,129,131,134(complete);4-8,42-57,62,80,81,88-90,92,95,98,99,102,118-120,122,125,128,130,133,136-139(partially).
See next page

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210
Subject 2: Claims 16-38,40,41,59-61,64-79,86,87,94,97,101,103,114-117,124,127, 132,135(complete); 4-8,42-57,62,80,81,88-90,92,95,98,99,102,118-120,122,125, 128,130,133,136-139(partially

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/US 96/20843

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0135349 A	27-03-85	WO 8500810 A	28-02-85
		WO 8505104 A	21-11-85
		WO 8600617 A	30-01-86
		AU 570710 B	24-03-88
		AU 3176184 A	14-02-85
		CA 1247611 A	27-12-88
		DE 3474959 A	08-12-88
		JP 1853504 C	07-07-94
		JP 60069073 A	19-04-85
		SU 1563593 A	07-05-90
		US 4548932 A	22-10-85
		US 4638000 A	20-01-87
		US 4591458 A	27-05-86
WO 9533751 A	14-12-95	US 5552400 A	03-09-96
		AU 2769995 A	04-01-96
		EP 0764167 A	26-03-97
		US 5639745 A	17-06-97
WO 9535308 A	28-12-95	US 5656627 A	12-08-97
		AU 2944695 A	15-01-96
		CA 2192089 A	28-12-95
		EP 0784628 A	23-07-97
		FI 965036 A	14-02-97
		NO 965365 A	17-02-97
		PL 318220 A	26-05-97
EP 0644198 A	22-03-95	AU 6347394 A	27-04-95
		CZ 9401355 A	15-12-94
		FI 942624 A	04-12-94
		HU 68689 A	28-07-95
		JP 7089951 A	04-04-95
		NO 942064 A	05-12-94
		NZ 260669 A	21-12-95
		SK 67394 A	11-07-95
		US 5585357 A	17-12-96
		HU 75964 A	28-05-97
WO 9526958 A	12-10-95	AU 2232395 A	23-10-95
		CA 2186511 A	12-10-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern ial Application No
PCT/US 96/20843

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9526958 A		EP 0752987 A	15-01-97
		FI 963897 A	27-09-96
		HU 75715 A	28-05-97
		NO 964058 A	26-09-96
EP 0618223 A	05-10-94	CA 2117121 A	09-09-94
		JP 6340691 A	13-12-94

Form PCT/ISA/210 (patent family annex) (July 1992)